NIH Public Access
Author Manuscript
J Expo Sci Environ Epidemiol. Author manuscript; available in PMC 2014 June 03.

Published in final edited form as:
J Expo Sci Environ Epidemiol. 2012 July ; 22(4): 393–397. doi:10.1038/jes.2012.19.

Effects of temperature, surfactants and skin location on the dermal penetration of haloacetonitriles and chloral hydrate

Maria Trabaris[1], **Jeffrey D. Laskin**[2], and **Clifford P. Weisel**[2]

[1]Joint Graduate Program in Exposure Assessment, Rutgers University - Graduate School of New Brunswick and UMDNJ - Graduate School of Biomedical Sciences, Piscataway, New Jersey, USA

[2]Department of Environmental and Occupational Medicine, Environmental and Occupational Health Sciences Institute, UMDNJ - Robert Wood Johnson Medical School, Piscataway, New Jersey, USA

Abstract

Dermal exposure has been recognized as an important contributor to the total internal dose to disinfection-by-products (DBPs) in water. However, the effect of the use of surfactants, water temperature and area of the body exposed to DBPs on their dermal flux has not been characterized and was the focus of the present study using an *in-vitro* system. The dermal flux of mg/l concentrations of haloacetonitriles and chloral hydrate (CH), important cytotoxic DBPs, increased by approximately 50% to 170% with increasing temperature from 25 °C to 40 °C. The fluxes for the torso and dorsum of the hand were much higher than that of palm and scalp skin. An increase in flux was observed for chloroacetonitrite and dichloroacetonitrile, two less lipophilic HANs, but not for trichloroacetonitrile or CH, with the addition of 2% sodium lauryl sulfate or 2% sodium laureth sulfate, two surfactants commonly used in soaps and shampoos used in showering and bathing. Thus, factors such as temperature, surfactants and skin location affect dermal penetration and should be considered when evaluating dermal absorption.

Keywords

dermal exposure; disinfection by-products; personal exposure

INTRODUCTION

Dermal exposure to disinfection-by-products (DBPs) occurs during showering, bathing and swimming. DBPs such as trihalomethanes (THMs), haloacetic acids, haloacetonitriles (HANs) and haloketones are formed by reactions of the disinfectant chlorine with humic substances and other organic material and are commonly found in tap and swimming pool water.[1–4] This study focuses on several factors that can alter the dermal absorption of the

© 2012 Nature America, Inc. All rights reserved

Correspondence to: Professor Clifford P. Weisel, Environmental and Occupational Health Sciences Institute, 170 Frelinghuysen Road, Piscataway, NJ 08854, USA. Tel: +732 445 0154. Fax: +732 445 0116. weisel@eohsi.rutgers.edu.

CONFLICT OF INTEREST The authors declare no conflict of interest.

NIH-PA Author Manuscript NIH-PA Author Manuscript NIH-PA Author Manuscript

NIH-PA Author Manuscript NIH-PA Author Manuscript NIH-PA Author Manuscript

DBPs: HANs and chloral hydrate (CH), among the most abundant DBPs in chlorinated drinking and swimming pool water.[5,6] The sum of their concentrations in tap water can be as high as 24 μg/l,[6,7] with much higher concentrations of dichloroacetonitrile (DCAN) and CH (45 μg/l and 265 μg/l, respectively) found in swimming pool water.[8] HANs and CH have been reported to be mutagenic and teratogenic and are of potential health concerns.[9–15] Epidemiological studies have linked DBPs, often using chloroform or THMs as surrogates for the DBPs, to cancer and adverse reproductive outcomes (as reviewed in Cantor,[16,17] Hrudey[18] and Tardiff et al.[19]). Dermal and/or inhalation exposure to THMs, as surrogates for DBPs, from showering and bathing had higher odds ratios for bladder cancer than was calculated for ingestion exposure in a case-control study, with an additional contribution to the odds ratio from THM exposure associated with swimming pool use.[20] Increased levels of genotoxicity biomarkers were also associated with exposure to brominated compounds in swimming pools, although distinguishing whether the exposure was through a dermal or inhalation route was not done.[21]

Based on biomarker measurements, dermal absorption has been documented to be an important contributor to the total daily dose of chloroform and other THMs, the DBPs with the highest pool and tap water concentrations[22–32] estimated that dermal exposure accounted for an average 64% of the total dose of lipophilic compounds in tap water during showering. Dermal absorption of several HANs and CH has been suggested to contribute 30–75% of their daily ingestion dose,[33] less than the THMs, but more than the haloacetic acids, the second most abundant DBPs in tap water.[34–37] Dermal exposure in swimming pools was estimated to be one-third of the dose for THMs under moderate exercise determined by comparing individuals wearing scuba gear who therefore only had dermal exposure, compared with individual swimming normally or breathing air next to the pool.[38] For highly competitive swimmers, it was reported that dermal exposure could contribute as much as 80% of the THM blood levels.[29]

Variations in the dermal absorption of an order of magnitude have been reported for hydrocortisone, pesticides and ^{32}P-labeled organic liquid phosphorous compounds across different areas of the body.[39–41] Thus, contact of different areas of the body with water could result in differential absorption of DBPs. Torso skin is the largest surface area exposed during showering, bathing and swimming, while the hand is exposed to water most frequently. An increase in dermal absorption of chloroform during showering with increasing water temperature has been reported,[25] which may result in lower dermal transport during swimming than showering as the temperature of pool water is often lower than used for showering and bathing. Surfactants, which are common components of soaps and shampoos used during showering and bathing, has been reported to affect dermal permeation[42] and induce skin irritation.[43] Two of the most common surfactants used are sodium laureth sulfate (SLES) and sodium lauryl sulfate (SLS). The current study evaluates the dermal flux of aqueous solution of HANs and CH at mg/l concentrations using *in-vitro* techniques with skin from different locations of the body, at 25 °C, 37 °C and 40 °C and with the use of surfactants.

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

METHODS

Skin Preparation

Human cadaver skin, obtained from the National Disease Research Interchange (Philadelphia, PA), was frozen before use, thus no metabolic activity was expected. Full-thickness human cadaver skin sections from different areas of the body were prepared by the removal of the subcutaneous tissue, leaving the dermis and epidermis. For some of the torso skin, the epidermis was separated from the dermis after submerging full-thickness skin in water heated to 60 °C for 1 min.[44] All skin sections were stored at −20 °C, a process not expected to affect their permeability characteristics.[45]

Skin Integrity

The physical integrity of a skin section was tested by determining the dermal flux for tritiated water.[44] If >0.29% of the applied tritiated water penetrated the skin after a 20-min exposure, the skin was considered to be damaged and not used. One hundred microliters of 10 μCi tritiated water (American Radiolabeled Chemicals, St. Louis, MO) was used for epidermal skin. Three hundred microliters of 10 μCi tritiated water was used to test whole skin. At the end of each time point, 100 μl of the receptor solutions were pipetted into 3 ml of Fisher Scientific ScintiVerse scintillation fluid in 5-ml scintillation vials. The vials were counted for radioactivity using a Packard TRI-CARB 2100TR liquid scintillation analyzer (Meridan, CT).

Experimental Procedures

The skin was thawed at room temperature in phosphate-buffered saline (PBS) solution and placed between two DC-100B side-by-side diffusion cells. The cells were completely mixed using Teflon-coated magnetic stirring bars spun at 600 r.p.m. The area of skin exposed in the diffusion cells was 0.636 cm^2. The receptor solution was a PBS solution at pH 7.4 maintained at 37 °C representing the body’s blood compartment. The donor solution was water containing the target DBP with or without a surfactant at 37 °C or without the surfactant at 25 °C, 37 °C or 40 °C. The range of temperatures encompasses those commonly used in bathing/showering and heated swimming pools. Heat-separated epidermal skin from the torso was used to study 1-hr exposures at differing temperatures and the effect of 2% surfactant solutions of SLES or SLS with donor cell HANs concentrations of 1 mg/l and 10 mg/l for CH. A 1-hr time frame was used as representative of the contact time during bathing or swimming. Studies comparing the effect of skin location examined dermal fluxes using full-thickness skin because the dermis could not be separated from the epidermis from the scalp section without tearing the skin. The whole-skin experiment used 3-hr exposures with donor cell HAN concentrations of 5 mg/l for CAN and DCAN, 15 mg/l for BCAN, 25 mg/l for DBAN and 100 mg/l for TCAN and CH. The 3-hr time frame was selected owing to the longer lag time for the compounds to penetrate the thicker whole skin to the receptor cell compared with the epidermis skin.

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

Sample Analysis

The HANs and CH were extracted from the saline or water with methyl-tert-butyl-ether and analyzed using US EPA Method 551.1. with iodoacetonitrile (98%) as an internal standard (Aldrich, Milwaukee, WI).[46] The extracts were injected into an HP5890 gas chromatograph (Hewlett-Packard, Santa Clara, CA) equipped with a 60-m Restek Rtx-624 capillary column (Bellefonte, PA), 0.25 mm i.d., 1.4 μm film thickness and an electron capture detector. Both the donor with the target DBPs and the receptor PBS solutions were sampled and replaced with fresh solutions at the end of the 1-hr experiment or every hour from the 3-hr experiments. This prevented the build-up of solutes in the receptor and maintained a constant donor concentration within ±20% of the expected value throughout the experiment. The flux (μg/hr-cm^2) was calculated directly from the amount of each compound present in the receptor solution, the time between the replacement of the receptor solution and the cross-sectional area of the exposed skin (0.636 cm^2).

Test Statistics

An ANOVA analysis was used to determine, for each compound separately, whether there were significant differences in the dermal flux with temperature, for skin from different locations in the body, and if surfactants were present. Newman–Keuls tests were used to compare the means for each condition.

RESULTS AND DISCUSSION

The stratum corneum (about 10–40 μm thick) is the main barrier against penetration of hydrophilic compounds, while the viable epidermis (about 100 μm thick) along with the dermis (about 10–40 μm thick) provide a barrier against lipophilic compounds.[47] Most compounds that penetrate the skin are quickly absorbed into the bloodstream through a capillary network above the dermis. Thus, using dermatomed skin to estimate dermal absorption provides a more accurate flux estimate than using whole skin. Whole-skin studies are useful in situations where dermatoming or using other methods to separate the epidermis from the dermis is ineffective. This is the case for experiments that compare skin absorption from different areas of the body. Removing the epidermis from scalp skin would leave holes in place of the hair follicles and result in erroneously high dermal flux estimates. While it may take longer for the compounds to penetrate the whole skin, permeability differences across experiments can still be compared as long as identical conditions are used. Therefore, whole skin was used for the *in-vitro* experiments involving skin obtained from different locations on the body.

Skin Location

Skin sections from the torso and the dorsum hand had higher dermal fluxes than the palm and scalp skin (Table 1). Generally, a thinner stratum corneum and a greater number of epidermal appendages, for example, hair follicles, results in greater skin permeability.[48] On most parts of the body, hair follicles have minimal effects on dermal absorption as they occupy only a small percentage of the surface area, <1–2% for abdominal skin.[48] However, this is not the case with scalp skin. Feldmann and Maibach[39] assessed hydrocortisone penetration through skin *in vivo* and observed that the scalp had the greatest permeation

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

followed by the back and palm. Maibach et al.[40] measured pesticide permeation *in vivo* and observed that the order of permeability was the scalp > dorsum hand > abdomen > palm. The lower dermal fluxes measured in the current study for the scalp using *in-vitro* techniques likely reflects the fact that penetration was measured across the full thickness (5 mm) of the skin, while for the human *in-vivo* studies, the compounds do not need to pass through the entire thickness of the scalp skin before entering the blood capillaries just below the hair follicles. This difference in permeation is consistent with the flux of tritiated compounds in hairless rats being 2–5 times lower than for normal rats.[49] The difference between hairless and normal rats is expected to be less than the difference between *in-vitro* and *in-vivo* human skin studies as rodent skin is far thinner (<1 mm) than full-thickness human scalp skin. The dermal flux of palm skin is much lower than other parts of the body owing to a thicker stratum corneum (0.4 mm to several mm), compared with the 10–40 μm thickness of stratum corneum of torso skin.[39,40,42,48] The total thickness of the skin samples used in these experiments was approximately 2 mm based on visual examination.

Temperature Effects

A variety of water temperatures are used during showering, bathing and in swimming pools. Based on exhaled breath measurements, it was observed that the apparent chloroform dose from bath water increased 30-fold when water temperature increased from 30 °C to 40 °C.[25,50] The authors suggested that the temperature effects were the result of changes in blood flow to the skin at different temperatures. An *in-vitro* permeability study using N-nitrosodiethanolamine showed an increase when the receptor cell temperature was increased from 32 °C to 37 °C.[51] Changes in the skin itself with temperature can also be responsible for increased permeability. In the current study, the skin permeability of HANs and CH was lowest when the donor-side temperature was 25 °C and increased as the donor temperature increased to 37 °C, and then to 40 °C (Table 2). The flux increased from approximately 50% to 170% as the temperature was increased from 25 °C to 40 °C for the compounds evaluated and were statistically different in the ANOVA and the Newman–Keuls *post-hoc* test at the 5% level for all compounds. One explanation for the change in skin permeability is that an increase in temperature increases the fluidity of the lipophilic layers between the corneocytes.[25,52] It has also been suggested that an increase in temperature affects the lipid viscosity by causing a transition of the lipid in the stratum corneum from a gel to a liquid-crystalline phase.[53] These results suggest that the higher *in-vivo* dermal dose of DBPs reported by Gordon et al.[25] from water at warmer temperatures may not only be due to an increase in blood flow to the skin, but also to an increase in the permeability characteristics of the skin. Thus, when estimating the contribution of dermal absorption the temperature of the water should be considered. Swimming pools typically have colder temperatures than used for showering or bathing, which could reduce the dose due to dermal penetration in swimming pools, compared with showering or bathing even though DBP concentrations are often higher in swimming pools.

Surfactants

Surfactants are commonly used while showering and bathing and may affect dermal permeability. The surfactants SLES and SLS, which are commonly used in soaps and shampoos, increased the permeation for CAN and DCAN, but not TCAN, BCAN or DBAN

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

(Table 3). Only SLS increased the flux of CH. Surfactants can disrupt the stratum corneum structure, the principal barrier to penetration of environmental contaminates. SLS was the only one of the four detergents (SLS, lutensol AP10, nonyl phenol ethoxylate and ethanol) to increase *in-vitro* penetration of tritiated water through human skin owing to its ability to compromise the integrity of the skin over a contact time of 4 hrs at concentrations of 0.2% and 2%.[54] SLS has also been reported to increase the permeability of compounds with lower lipophilicities (log Kow <3).[55] Surfactants are added to soaps and shampoos as they have both a polar and a non-polar end, this assists the dissolution of lipophilic compounds, such as grease and dirt, into an aqueous solution. This functionality will also facilitate the penetration of hydrophilic compounds through lipid membranes.[54] Because the stratum corneum includes a lipid matrix, the presence of a surfactant appeared to facilitate the permeability of the least lipophilic HANs evaluated: CAN and DCAN.

Extrapolation to Environmental Concentrations

It is important to recognize that the mg/l concentrations used in this study greatly exceed the levels measured in either tap water or swimming pool water. As recently discussed, the dermal flux could be dependent upon the concentration, with lower concentrations having higher dermal fluxes.[56] The flux also changes with time until steady state is reached which can exceed the 1–3 hrs used.[33] Thus, if the dermal flux for these compounds varies with concentration as suggested by Kissel,[56] then the magnitude of the effect observed may be different at lower concentrations but is expected that direction of the effects would be the same across concentration ranges.

CONCLUSIONS

An increase in temperature increased skin permeability. The two surfactants, SLS and SLES, increased the permeability of CAN and DCAN, the HANs with the greatest solubility in water and the lowest lipophilic nature. The dorsum hand and torso skin were much more permeable than the palm skin because of the greater thickness of the stratum corneum in the palm and the scalp. However, these values may not be applicable *in vivo* as compounds can enter the blood stream without traversing the entire thickness of the epidermis. These data indicated that an individual’s activities, which part of the body contacts water, the use of shampoos and the water temperature during bathing, showering and swimming alter the degree of dermal absorption of the DBPs and other contaminants in tap water. The magnitude of the effect at environmentally relevant water concentrations still needs to be determined to accurately predict the actual flux of DBP present in chlorinated water to assess their risk.

Acknowledgments

This research was funded by the United States Environmental Protection Agency (US EPA) Research Foundation (#GR825953-01-0). This presentation has not been subjected to the Agency’s review and therefore may not necessarily reflect the views of the Agency. CPW and JL are supported in part by NIEHS Center of Excellence (P30ES005022). This research was also supported by the CounterACT Program, National Institutes of Health, Office of the Director, and the National Institute of Arthritis and Musculoskeletal and Skin Diseases, Grant number AR055073. We also thank Thomas M. Mariano from the Environmental and Occupational Health Sciences Institute, Department of Environmental and Occupational Medicine and UMDNJ- Robert Wood Johnson Medical

School, Piscataway, New Jersey for his valuable help with handling radiolabeled compounds and the National Disease Research Interchange (NDRI) in Philadelphia, PA for providing the skin samples used in this study.

REFERENCES

1. Krasner S, Mcguir M, Jacangelo J, Patania N, Reagan K, Aieta E. The occurrence of disinfection by-products in US drinking water. J Am Water Works Assoc. 1989; 81:41–53.
2. Pressman JG, Richardson SD, Speth TF, Miltner RJ, Narotsky MG, Hunter ES 3rd, Rice GE, Teuschler LK, McDonald A, Parvez S, Krasner SW, Weinberg HS, McKague AB, Parrett CJ, Bodin N, Chinn R, Lee C-FT, Simmons JE. Concentration, chlorination, and chemical analysis of drinking water for disinfection byproduct mixtures health effects research: U.S. EPA's Four Lab Study. Environ Sci Technol. 2010; 44:7184–7192. [PubMed: 20496936]
3. Richardson, S. Drinking Water Disinfection By-products. The Encyclopedia of Environmental Analysis and Remediation. Vol. Vol 3. Wiley; New York: 1998.
4. Richardson SD, DeMarini DM, Kogevinas M, Fernandez P, Marco E, Lourencetti C, Balleste C, Heederik D, Meliefste K, McKague AB, Marcos R, Font-Ribera L, Grimalt JO, Villanueva CM. What's in the pool? A comprehensive identification of disinfection by-products and assessment of mutagenicity of chlorinated and brominated swimming pool water. Environ Health Perspect. 2010; 118:1523–1530. [PubMed: 20833605]
5. Kim H, Shim J, Lee S. Formation of disinfection by-products in chlorinated swimming pool water. Chemosphere. 2002; 46:123–130. [PubMed: 11806524]
6. Krasner SW, Weinberg HS, Richardson SD, Pastor SJ, Chinn R, Sclimenti MJ, Onstad GD, Thruston AD Jr. Occurrence of a new generation of disinfection byproducts. Environ Sci Technol. 2006; 40:7175–7185. [PubMed: 17180964]
7. Bull, RJ.; Kopfler, FC. Health Effects of Disinfection By-Products. AWWA research foundation and American water works association; Denver, Co: 1991.
8. World Health Organization. Chemical Hazards. Guidelines for Safe Recreational-Water Environments. Chapter 4. 2000. http://www.who.int/water_sanitation_health/bathing/recreaII-ch4.pdf
9. Bull RJ, Meier JR, Robinson M, Ringhand HP, Laurie RD, Stober JA. Evaluation of mutagenic and carcinogenic properties of brominated and chlorinated acetonitriles: by-products of chlorination. Fundam Appl Toxicol. 1985; 5:1065–1074. [PubMed: 4092869]
10. Daniel FB, Schenck KM, Mattox JK, Lin EL, Haas DL, Pereira MA. Genotoxic properties of haloacetonitriles: drinking water by-products of chlorine disinfection. Fundam Appl Toxicol. 1986; 6:447–453. [PubMed: 3699330]
11. Lin EL, Daniel FB, Herren-Freund SL, Pereira MA. Haloacetonitriles: metabolism, genotoxicity, and tumor-initiating activity. Environ Health Perspect. 1986; 69:67–71. [PubMed: 3816737]
12. Nouraldeen AM, Ahmed AE. Studies on the mechanisms of haloacentronitrile-induced genotoxicity IV: *in vitro* interaction of haloacetonitriles with DNA. Toxicol In Vitro. 1996; 10:17–26. [PubMed: 20650178]
13. Smith MK, Randall JL, Stober JA, Read EJ. Developmental toxicity of dichloroacetonitrile: a by-product of drinking water disinfection. Fundam Appl Toxicol. 1989; 12:765–772. [PubMed: 2744278]
14. Smith MK, Zenick H, George EL. Reproductive toxicology of disinfection by-products. Environ Health Perspect. 1986; 69:177–182. [PubMed: 2949968]
15. Valencia R, Mason JM, Woodruff RC, Zimmering S. Chemical mutagenesis testing in Drosophila. III. Results of 48 coded compounds tested for the National Toxicology Program. Environ Mutagen. 1985; 7:325–348. [PubMed: 3930234]
16. Cantor KP. Drinking water and cancer. Cancer Causes Cont. 1997; 8:292–308.
17. Cantor KP. Carcinogens in drinking water: the epidemiologic evidence. Rev Environ Health. 2010; 25:9–16. [PubMed: 20429153]
18. Hrudey SE. Chlorination disinfection by-products, public health risk tradeoffs and me. Water Res. 2009; 43:2057–2092. [PubMed: 19304309]

NIH-PA Author Manuscript NIH-PA Author Manuscript NIH-PA Author Manuscript

NIH-PA Author Manuscript
NIH-PA Author Manuscript
NIH-PA Author Manuscript

19. Tardiff RG, Carson ML, Ginevan ME. Updated weight of evidence for an association between adverse reproductive and developmental effects and exposure to disinfection by-products. Regulat Toxicol Pharmacol. 2006; 45:185–205.
20. Villanueva CM, Cantor KP, Grimalt JO, Malats N, Silverman D, Tardon A, Garcia-Closas R, Serra C, Carrato A, Castano-Vinyals G, Marcos R, Rothman N, Real FX, Dosemeci M, Kogevinas M. Bladder cancer and exposure to water disinfection by-products through ingestion, bathing, showering, and swimming in pools. Am J Epidemiol. 2007; 165:148–156. [PubMed: 17079692]
21. Kogevinas M, Villanueva CM, Font-Ribera L, Liviac D, Bustamante M, Espinoza F, Nieuwenhuijsen MJ, Espinosa A, Fernandez P, DeMarini DM, Grimalt JO, Grummt T, Marcos R. Genotoxic effects in swimmers exposed to disinfection by-products in indoor swimming pools. Environ Health Perspect. 2010; 118:1531–1537. [PubMed: 20833606]
22. Backer LC, Ashley DL, Bonin MA, Cardinali FL, Kieszak SM, Wooten JV. Household exposures to drinking water disinfection by-products: whole blood trihalomethane levels. J Expo Anal Environ Epidemiol. 2000; 10:321–326. [PubMed: 10981726]
23. Brown HS, Bishop DR, Rowan CA. The role of skin absorption as a route of exposure for volatile organic compounds (VOCs) in drinking water. Am J Public Health. 1984; 74:479–484. [PubMed: 6711723]
24. Font-Ribera L, Kogevinas M, Zock J-P, Gomez FP, Barreiro E, Nieuwenhuijsen MJ, Fernandez P, Lourencetti C, Perez-Olabarria M, Bustamante M, Marcos R, Grimalt JO, Villanueva CM. Short-term changes in respiratory biomarkers after swimming in a chlorinated pool. Environ Health Perspect. 2010; 118:1538–1544. [PubMed: 20833607]
25. Gordon SM, Wallace LA, Callahan PJ, Kenny DV, Brinkman MC. Effect of water temperature on dermal exposure to chloroform. Environ Health Perspect. 1998; 106:337–345. [PubMed: 9618350]
26. Jo WK, Weisel CP, Lioy PJ. Chloroform exposure and the health risk associated with multiple uses of chlorinated tap water. Risk Anal. 1990a; 10:581–585. [PubMed: 2287785]
27. Jo WK, Weisel CP, Lioy PJ. Routes of chloroform exposure and body burden from showering with chlorinated tap water. Risk Anal. 1990b; 10:575–580. [PubMed: 2287784]
28. Leavens TL, Blount BC, DeMarini DM, Madden MC, Valentine JL, Case MW, Silva LK, Warren SH, Hanley NM, Pegram RA. Disposition of bromodichloromethane in humans following oral and dermal exposure. Toxicol Sci. 2007; 99:432–445. [PubMed: 17656487]
29. Lindstrom AB, Pleil JD, Berkoff DC. Alveolar breath sampling and analysis to assess trihalomethane exposures during competitive swimming training. Environ Health Perspect. 1997; 105:636–642. [PubMed: 9288498]
30. Nuckols JR, Ashley DL, Lyu C, Gordon SM, Hinckley AF, Singer P. Influence of tap water quality and household water use activities on indoor air and internal dose levels of trihalomethanes. Environ Health Perspect. 2005; 113:863–870. [PubMed: 16002374]
31. Weisel CP, Jo WK. Ingestion, inhalation, and dermal exposures to chloroform and trichloroethene from tap water. Environ Health Perspect. 1996; 104:48–51. [PubMed: 8834861]
32. Weisel, CP.; Shepard, T. Chloroform and the Resulting Body Burden Associated with Swimming in Chlorinated Pools. Marcel Dekker, Inc.; New York: 1994.
33. Trabaris M, Laskin JD, Weisel CP. Percutaneous absorption of haloacetonitriles and chloral hydrate and simulated human exposures. J Appl Toxicol. e-pub ahead of print 1 March 2011.
34. Bader EL, Hrudey SE, Froese KL. Urinary excretion half life of trichloroacetic acid as a biomarker of exposure to chlorinated drinking water disinfection byproducts. Occup Environ Med. 2004; 61:715–716. [PubMed: 15258281]
35. Xu X, Mariano TM, Laskin JD, Weisel CP. Percutaneous absorption of trihalomethanes, haloacetic acids, and haloketones. Toxicol Appl Pharmacol. 2002; 184:19–26. [PubMed: 12392965]
36. Xu X, Weisel CP. Dermal uptake of chloroform and haloketones during bathing. J Expo Anal Environ Epidemiol. 2005; 15:289–296. [PubMed: 15316574]
37. Zhang WP, Gabos S, Schopflocher D, Li XF, Gati WP, Hrudey SE. Reliability of using urinary and blood trichloroacetic acid as a biomarker of exposure to chlorinated drinking water disinfection byproducts. Biomarkers. 2009; 14:355–365. [PubMed: 19583459]

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

38. Erdinger L, Kuhn KP, Kirsch F, Feldhues R, Frobel T, Nohynek B, Gabrio T. Pathways of trihalomethane uptake in swimming pools. Int J Hyg Environ Health. 2004; 207:571–575. [PubMed: 15729838]
39. Feldmann RJ, Maibach HI. Regional variation in percutaneous penetration of 14C cortisol in man. J Invest Dermatol. 1967; 48:181–183. [PubMed: 6020682]
40. Maibach HI, Feldman RJ, Milby TH, Serat WF. Regional variation in percutaneous penetration in man. Pesticides. Arch Environ Health. 1971; 23:208–211. [PubMed: 5123154]
41. Marzulli FN. Barriers to skin penetration. J Invest Dermatol. 1962; 39:387–393. [PubMed: 13933249]
42. Scheuplein RJ, Blank IH. Permeability of the skin. Physiol Rev. 1971; 51:702–747. [PubMed: 4940637]
43. Howes D. The percutaneous absorption of some anionic surfactants. J Soc Cosmet Chemists. 1975; 26:47–63.
44. Bronaugh RL, Stewart RF, Simon M. Methods for *in vitro* percutaneous absorption studies. VII: use of excised human skin. J Pharm Sci. 1986; 75:1094–1097. [PubMed: 3820104]
45. Harrison SM, Barry BW, Dugard PH. Effects of freezing on human skin permeability. J Pharm Pharmacol. 1984; 36:261–262. [PubMed: 6144776]
46. US EPA. Method 551.1. Determination of Chlorination Disinfection Byproducts, Chlorinated Solvents, and Halogenated Pesticides/Herbicides in Drinking Water by Liquid-Liquid Extraction and Gas Chromatography with Electron-Capture Detection. National Exposure Research Laboratory, Office of Research and Development; Cincinnati, OH: 1995. Revision 1.0
47. US EPA. Dermal Exposure Assessment: Principles and Applications. U.S. Environmental Protection Agency; Washington, DC: 1992. 〈 http://nepis.epa.gov/Exe/ZyPURL.cgi?Dockey=30001L2F.txt 〉
48. Bunge, AL.; McDougal, JN. Exposure to Contaminants in Drinking Water-Estimating Update Through the Skin and by Inhalation. International Life Science Institute; Washington, DC: 1999. Dermal Uptake.
49. Illel B, Schaefer H, Wepierre J, Doucet O. Follicles play an important role in percutaneous absorption. J Pharm Sci. 1991; 80:424–427. [PubMed: 1880719]
50. Corley RA, Gordon SM, Wallace LA. Physiologically based pharmacokinetic modeling of the temperature-dependent dermal absorption of chloroform by humans following bath water exposures. Toxicol Sci. 2000; 53:13–23. [PubMed: 10653516]
51. Franz TJ, Lehman PA, Franz SF, North-Root H, Demetrulias JL, Kelling CK, Moloney SJ, Gettings SD. Percutaneous penetration of N-nitrosodiethano-lamine through human skin (*in vitro*): comparison of finite and infinite dose applications from cosmetic vehicles. Fundam Appl Toxicol. 1993; 21:213–221. [PubMed: 8405784]
52. Ogiso T, Ogiso H, Paku T, Iwaki M. Phase transitions of rat stratum corneum lipids by an electron paramagnetic resonance study and relationship of phase states to drug penetration. Biochim Biophys Acta. 1996; 1301:97–104. [PubMed: 8652657]
53. Ogiso T, Hirota T, Iwaki M, Hino T, Tanino T. Effect of temperature on percutaneous absorption of terodiline, and relationship between penetration and fluidity of the stratum corneum lipids. Inter J Pharm. 1998; 176:63–72.
54. Nielson JB. Effects of four detergents on the *in-vitro* barrier function of human skin. Int J Occup Environ Health. 2000; 6:143–147. [PubMed: 10828144]
55. Borras-Blasco, J.e.a Influence of sodium lauryl sulphate on the *in vitro* percutaneous absorption of compounds with different lipophilicity. Eur J Pharm. 1997; 5:15–22.
56. Kissel JC. The mismeasure of dermal absorption. J Expo Sci Environ Epidemiol. 2011; 21:302–309. [PubMed: 20424648]

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

Table 1

Dermal flux for different parts of the body calculated for 3-hr exposures with both side-by-side cells heated to 37 °C±1 °C with the whole skin exposed to 5 mg/l of CAN and DCAN, 15 mg/l of BCAN, 25 mg/l of DBAN, and 100 mg/l of TCAN and CH solutions (n=3).

Surface area of body (%)[a]		Flux (mg/hr-cm^2), (mean and SD)					
		CAN	DCAN	TCAN	BCAN	DBAN	CH
Scalp	5.10	0.015±0.028	ND	ND	ND	0.022±0.0053	0.0023±0.00044
Palm	2.60	0.044±0.038	0.068±0.017	ND	0.0018±0.00040	0.038±0.0075[b]	0.012±0.0022[b]
Torso	35[c]	0.27±0.064[b]	0.25±0.066[b]	0.63±0.13[b]	0.54±0.085[b]	0.97±0.21[b]	0.089±0.16[b]
Dorsum	2.60	0.42±0.097[b]	0.32±0.080[b]	0.91±0.20[b]	0.53±0.076[b]	0.82±0.16[b]	0.098±0.014[b]

ND, not detected.

[a]Source: US EPA.[47]

[b]These means were found to be significantly higher than next lower group at the 5% level using the Newman–Keuls test that tests multiple means.

[c]Excludes extremities (upper 19%, lower 38%.

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

Table 2

Dermal flux as a function of temperature after a 1-hr exposure using heat-separated epidermal torso skin exposed to 1 mg/l of the HANs and 10 mg/l of CH solutions (*n*=3).

Temperature	Flux (mg/hr-cm^2), (mean and SD)					
	CAN	DCAN	TCAN	BCAN	DBAN	CH
25 °C±1 °C	0.052±0.0092	0.064±0.010	0.053±0.0082	0.076±0.011	0.075±0.0098	0.020±0.0045
37 °C±1 °C[a]	0.083±0.012	0.10±0.022	0.079±0.014	0.12±0.018	0.15±0.024	0.037±0.0061
40 °C±1 °C	0.091±0.014	0.12±0.025	0.083±0.013	0.13±0.020	0.16±0.026	0.053±0.0081
% Increase between 25 °C and 40 °C	75	88%	57	71	110	170

The fluxes for all compounds were statistically different at the 5% level using the Newman–Keuls test that tests multiple means.

[a]Same data as in Table for no surfactant.

NIH-PA Author Manuscript
NIH-PA Author Manuscript
NIH-PA Author Manuscript

Table 3

Dermal flux calculated after a 1-hr exposure using heat separated epidermal skin with both cells heated to 37 °C±1 °C.

Surfactant	Flux (mg/hr-cm^2) (mean and SD)					
	CAN	DCAN	TCAN	BCAN	DBAN	CH
No surfactant[a]	0.083±0.012	0.10±0.022	0.079±0.014	0.12±0.018	0.15±0.024	0.037±0.0061
SLES	0.18±0.029[b]	0.25±0.071[b]	0.094±0.013	0.10±0.016	0.18±0.027	0.025±0.0042
SLS	0.21±0.054[b]	0.71±0.182[b,c]	0.085±0.011	0.14±0.019	0.17±0.026	0.082±0.012[b]

The skin was exposed to 1 mg/l of the HANs and 10 mg/l of CH solutions with or without the surfactants sodium laureth sulfate (SLES) and sodium lauryl sulfate (SLS; *n*=3).

[a]Same data as in Table 2 for 37 °C.

[b]These means were found to be significantly higher at the flux with no surfactant at the 5% level using the Newman–Keuls test that tests multiple means.

[c]This mean was found to be significantly higher than the SLES mean at the 5% level using the Newman–Keuls test.