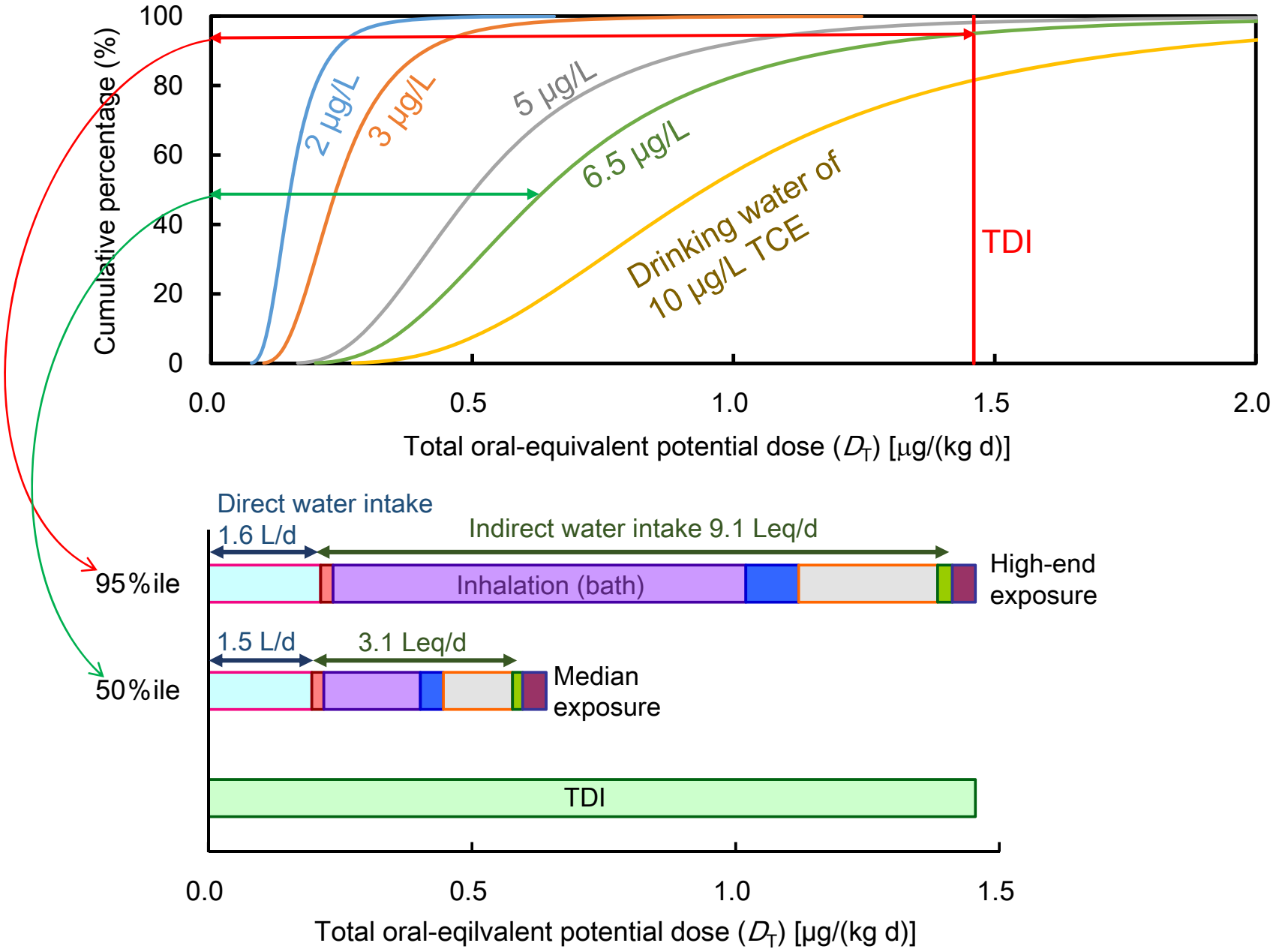
Highlights

- Concentrations resulting in total dose < TDI for majority population were estimated.
- More stringent concentration than the current standard was suggested for TCE.
- Indirect inhalation exposure was major exposure route for the THMs, TCE, and PCE.
- Ingestion of food was a major indirect route for HAAs.
- Indirect exposure accounted for 1.2 to 9 Leq/day.


Cumulative percentage (%)
100
80
60
40
20
0
2 µg/L
3 µg/L
5 µg/L
6.5 µg/L
Drinking water of
10 µg/L TCE
TDI
0.0
0.5
1.0
1.5
2.0
Total oral-equivalent potential dose (D_T) [µg/(kg d)]
Direct water intake
1.6 L/d
Indirect water intake 9.1 Leq/d
95%ile
Inhalation (bath)
High-end
exposure
1.5 L/d
3.1 Leq/d
50%ile
Median
exposure
TDI
0.0
0.5
1.0
1.5
Total oral-eqilvalent potential dose (D_T) [µg/(kg d)]

Monte-Carlo and multi-exposure assessment for the derivation of criteria for disinfection byproducts and volatile organic compounds in drinking water: allocation factors and liter-equivalents per day

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Abstract

The probability distributions of total potential doses of disinfection byproducts and volatile organic compounds via ingestion, inhalation, and dermal exposure were estimated with Monte Carlo simulations, after conducting physiologically based pharmacokinetic model simulations to takes into account the differences in availability between the three exposures. If the criterion that the 95th percentile estimate equals the TDI (tolerable daily intake) is regarded as protecting the majority of a population, the drinking water criteria would be 140 (trichloromethane), 66 (bromodichloromethane), 157 (dibromochloromethane), 203 (tribromomethane), 140 (dichloroacetic acid), 78 (trichloroacetic acid), 6.55 (trichloroethylene, TCE), and 22 μg/L (perchloroethylene). The TCE criterion was lower than the Japanese Drinking Water Quality Standard (10 μg/L). The latter would allow the intake of 20% of the population to exceed the TDI. Indirect inhalation via evaporation from water, especially in bathrooms, was the major route of exposure to compounds other than haloacetic acids (HAAs) and accounted for 1.2–9 liter-equivalents/day for the median-exposure subpopulation. The ingestion of food was a major indirect route of exposure to HAAs. Contributions of direct water intake were not very different for trihalomethanes (30–45% of TDIs) and HAAs (45–52% of TDIs).

Keywords:

Water quality standard

THM

HAA

TCE

PCE

1. Introduction

The health-based drinking water quality criterion for a chemical that has a threshold for its toxicity is derived from the tolerable daily intake (TDI), drinking water intake, and allocation factor (or relative source contribution), which is the fraction of the TDI allocated to intake of drinking water (WHO, 2011). The derivation is based on the concept that the sum of the daily total exposures from multiple sources should be within the TDI.

When the contribution of water to total daily exposure is unknown, a low value, 10 or 20%, of the allocation factor is traditionally used as a default value based on the protective policy that any additional exposure from water to total exposure should be negligible (Howd et al., 2004; Krishnan and Carrier, 2013). The use of a low allocation factor is believed to be “generous” to accommodate and account for additional routes of uptake in most cases (Health Canada, 1995; Krishnan and Carrier, 2013). This policy can be interpreted to mean that water, as a human necessity, should not become a major source of exposure, even if there is no significant exposure from other sources. Therefore, a low value of the allocation factor is applied as long as the health-based drinking water quality criterion derived with the low allocation factor is practically and technically feasible.

An allocation factor other than the low default value is, however, sometimes required, for example when the chemical agent is mainly present in drinking water. An appropriate value of the allocation factor can be used to ensure that an individual’s total exposure from multiple sources does not exceed the TDI. However, total exposure varies from one individual to another within a population. Moreover, drinking water intake also varies individually, although the default intake value of 2 L/d is widely and traditionally used in the derivation of health-based drinking water quality criteria. Use of a range of appropriate intake values is expected to result in a criterion that is protective of a majority of the population.

In the subtraction method of the specific RSC (Relative Source Contribution) approach, sometimes called an Exposure Decision Tree (Gadagbui et al., 2012; USEPA, 2000), sources of exposure other than drinking water and fish can be considered as background and can be subtracted from the TDI. The estimates of intake from non-water exposures are based on arithmetic mean values of the variable intake of individuals, and the drinking water and fish intake values are 90th percentile estimates. The estimated 90th percentiles of the distributions of daily average per-capita water ingestion by the U.S. population are 2.014 L of community water and 2.341 L of water from all sources (USEPA, 2004). Although these assumptions are likely protective of a majority of the population, the extent to which they are protective has not been quantitatively determined.

Inhalation and dermal exposures via volatilization of water and dermal contact with water, respectively, are important routes of exposure, in particular for volatile and/or hydrophobic contaminants such as chloroform (Krishnan and Carrier, 2008; Wallace, 1997). These exposures are evaluated in terms of liter-equivalents per day (Leq/d). The use of Leq's as metrics of exposure is the most appropriate approach in the case of systemically acting contaminants that do not exhibit portal-of-entry effects but are likely to induce the same adverse effect by various exposure routes (Krishnan and Carrier, 2008). When considering the sum of each daily total exposure from multiple sources in multi-exposure assessments by methods such as the Leq approach, improvements are still envisioned based on consideration of bioavailability, target tissue dose, and extent of absorption via all routes and media (Krishnan and Carrier, 2013).

Values of Leq/d are actually used to establish drinking water quality criteria in the case of compounds of health concern such as trihalomethanes (Health Canada, 2006). For volatile organic compounds (VOCs), including trihalomethanes (THMs), tetrachloroethylene (perchloroethylene, PCE, IUPAC name: tetrachloroethene), and trichloroethylene (TCE, IUPAC name: trichloroethene), McKone (1987) has estimated that the indoor-air exposure

attributable to tap water is 1.5–6 times the exposure attributable to the consumption of 2 L/d of tap water. Weisel and Jo (1996) have reported that approximately equivalent amounts of the volatile contaminants trichloromethane (TCM) and TCE in water can enter the body by three different exposure routes—inhalation, dermal absorption, and ingestion—as a result of the typical daily activities of drinking and bathing. Jo et al. (2005) have reported that exposure estimates to the THMs [TCM, bromodichloromethane (BDCM), dibromochloromethane (DBCM), and tribromomethane (TBM)] from ingestion of tap water were similar to those from showering. Xu et al. (2002) have suggested that the daily dermal dose of the THMs was approximately 40–70% of the dose from ingestion, while that of haloacetic acids (HAAs) was an insignificant fraction of the daily dose from ingestion. Yanagibashi (2010) has estimated the percentage contribution of ingestion via drinking water to total THM exposure to be 4–24%; the analogous percentages from exposure via inhalation and dermal absorption were 69–94%. These results show that inhalation and dermal contact exposure attributable to tap water may result in exposure equal to or much larger than the exposure from water intake. If the exposures derived from these analyses are converted to units of Leq/d, the total exposure to THMs could be 3–30 Leq/d. The indirect water intake rates (Leq/d values) are basically dependent on exposure scenarios, such as the duration of showering. Therefore, the wide range of the values (3–30 Leq/d) could be partly due to the exposure scenarios assumed. After all, the Leq/d values as well as other intake estimates are associated with a distribution of lifestyles within the population.

Finally, a wide range of intakes from multiple sources is associated with the distributions of lifestyles in a population. Considering the variability of the intakes between individuals, the derivation of Leq's as well as the allocation factor should probably be based on the concept that the sum of the daily total exposures of each individual from all sources should be within the TDI. Whereas the combination of appropriate intake values is expected to result in a criterion

that protects a majority of the population, it is quite possible that combining all the high-end intakes for every exposure source is too protective. An approach to characterize the population distribution of intake is the use of probabilistic models that account for the variability of the input parameters related to the exposure scenarios of the population.

Niizuma et al. (2013) have conducted assessments of multiple-route exposures to TCM by using a Monte-Carlo approach to create exposure scenarios. They have estimated TCM criteria that provide protection for a majority (95th percentile) of the population. However, their approach has not been used and verified for other contaminants. In their study, moreover, they assumed a constant drinking water consumption rate of 2 L/d for a 50-kg person, but they did not conduct assessments that took into consideration the distributions of daily drinking water intake and body weight.

The objective of this study was to extend the multi-route exposure assessment method of Niizuma et al. (2013) by taking into consideration the distributions of daily drinking water intake and body weight. The assessment method was applied to eight compounds for which physiologically based pharmacokinetic (PBPK) models were available (Table 1). Six compounds were volatile; the other two were not volatile. Six compounds were disinfection byproducts (DBPs). Drinking water quality criteria and Leq/d values that provided protection for a majority (95th percentile) of the population were determined, and allocation factors were discussed. The results were then compared between the eight compounds. Total exposure from multiple sources was evaluated based on the chemical burden in the target organ by using the concept of oral-equivalent potential dose, which takes into account the differences in availability: the ratio of the biologically effective dose at the site of toxic action per potential dose (administered dose) via oral exposure, inhalation, or dermal exposure.

2. Methods

2.1. Total oral-equivalent potential dose

Exposure route is important in determining toxicity. Ingested compounds are metabolized during the first pass through the liver, whereas inhaled and dermally permeated compounds pass directly into the general circulation (Weisel and Jo, 1996). Therefore, simple summation of potential exposure or administrated dose is not appropriate, even if a target compound induces the same adverse effect by multiple exposure routes. It is necessary to know the biologically effective dose at the site of activity (a target organ) of a contaminant. A PBPK model relates the potential exposure to the biologically effective dose (Wallace, 1997).

Niizuma et al. (2013) have conducted a PBPK model simulation of TCM to calculate equal biologically effective doses from potential exposures via various exposure routes. They proposed an equation for total oral-equivalent potential dose via three routes (oral ingestion, inhalation, and dermal exposure). The oral-equivalent potential dose is a normalized potential dose in which a biologically effective dose associated with inhalation or dermal exposure is converted into a hypothetical potential dose from oral ingestion with the same equivalent biologically effective dose. For example, when the oral-equivalent potential dose of inhalation is 1 mg/(kg d), that dose produces the same biologically effective dose as an oral potential dose of 1 mg/(kg d). The total oral-equivalent potential dose via three routes (oral ingestion, inhalation, and dermal exposure) is given by (Niizuma et al., 2013):

$$D_{\mathrm{T}} = \frac{A_{\mathrm{D}}}{b_{\mathrm{w}}} + R_{2/1}\frac{\overline{C_{\mathrm{a}}}\phi Q}{b_{\mathrm{w}}} + R_{3/1}\frac{K_{\mathrm{p}}A_{\mathrm{sk}}\overline{C_{\mathrm{d}}}}{b_{\mathrm{w}} \times 1000\ \mathrm{cm^3/L}} \qquad (1)$$

The value of the relative availability for inhalation/oral exposure ($R_{2/1}$) was estimated by

using Equation (2) with the results of PBPK model simulation.

$$R_{2/1} = \left(\frac{A_{\text{oral}}}{AUC_{\text{oral}}/t_{\text{oral}}}\right) \cdot \left(\frac{AUC_{\text{inhalation}}/t_{\text{inhalation}}}{C_{\text{inhalation}} Q_{alv}}\right) \quad (2)$$

Similarly, the value of the relative availability for dermal/oral exposure ($R_{3/1}$) was estimated by using Equation (3).

$$R_{3/1} = \left(\frac{A_{\text{oral}}}{AUC_{\text{oral}}/t_{\text{oral}}}\right) \cdot \left(\frac{AUC_{\text{dermal}}/t_{\text{dermal}}}{C_{\text{dermal}} K_{\text{p}} A_{\text{sk}} \times 10^{-3}\, L/\text{cm}^3}\right) \quad (3)$$

For the estimations of the AUC (area under the curve) values of the THMs, we used the same PBPK model as that of Niizuma et al. (2013), which is structurally similar to previous models (Corley et al., 2000; Corley et al., 1990; Ramsey and Andersen, 1984; Tan et al., 2006b) (Fig. SA1, Table SA1-1, and Table SA1-2, Supplementary Information A). The TDIs of THMs are determined from administered doses based on the incidence of hepatic cysts (Table 2). Hepatic cytotoxicity following exposure to THM is primarily related to rates of THM metabolism (Lévesque et al., 2000; Lévesque et al., 2002; Liao et al., 2007; Reitz et al., 1990; Sasso et al., 2013; Tan et al., 2003). Therefore, the AUCs were obtained in plots of the rates of THM metabolism in liver vs. time.

For dichloroacetic acid (DCAA), we applied the model of Li et al. (2008) after incorporating a component for dermal adsorption (Poet et al., 2000) (Fig. SA3, Table SA3-1, and Table SA3-2, Supplementary Information A). For trichloroacetic acid (TCAA), we applied the model of Fisher et al. (1998) after incorporating a component for dermal adsorption (Poet et al., 2000) (Fig. SA2, Table SA2-1, and Table SA2-2, Supplementary

Information A). Because the TDI values of the HAAs were determined on the basis of hepatic toxicity (Table 3), the AUCs were obtained in plots of the HAA concentrations in the venous blood leaving the liver vs. time.

For TCE, we applied published models (Clewell et al., 2000; Clewell et al., 2001; Fisher et al., 1998) after incorporating a component for dermal adsorption (Poet et al., 2000) (Fig. SA4, Table SA4-1, and Table SA4-2, Supplementary Information A). For PCE, we applied published models (Clewell et al., 2001; Covington et al., 2007; Fisher et al., 1998) after incorporating a component for dermal adsorption (Poet et al., 2000; Poet et al., 2002) (Fig. SA5, Table SA5-1, and Table SA5-2, Supplementary Information A). Because the TDI value of the TCE is determined on the basis of developmental toxicity to the fetal heart and the developmental toxicity is associated with TCE's metabolites, trichloroacetic acid (TCAA) (Johnson et al., 1998a; Johnson et al., 1998b; USEPA, 2011a; USEPA, 2011b) and dichloroacetic acid (DCAA) (Epstein et al., 1992; Smith et al., 1992; USEPA, 2003), the AUCs were obtained in plots of the TCAA and DCAA concentrations in placenta vs. time, as well as in the plots of TCE concentration vs. time, after the administration of TCE (Table 2 and Table SB1, Supplementary Information B).

The TDI of PCE was determined based on the incidence of hepatic cysts and the hepatotoxic effect is thought to be due to the PCE's metabolite, TCAA (USEPA, 2012; WHO, 2003). The AUCs for PCE were, therefore, obtained in plots of the TCAA concentrations in the venous blood leaving the liver vs. time, as well as in the plots of PCE concentration vs. time, after the administration of PCE.

The PBPK models were solved with the relevant parameter values (Supplementary Information B) by using Mathematica 10 (Wolfram Research, Champaign, IL, USA) to estimate AUC values, and then the values of $R_{2/1}$ and $R_{3/1}$ were estimated from the AUC values by using equation (2) and (3), respectively.

222

223 *2.3. Monte-Carlo and multi-exposure assessment*

224

225 We calculated the probability distribution functions for total oral-equivalent exposure via the
226 three routes (ingestion via drinking water and food, inhalation, and dermal absorption) by using
227 Equation (1) for given concentrations of target compounds in drinking water and Monte Carlo
228 inputs (Crystal Ball 2000, Japanese edition, Kozo Keikaku Engineering Inc., Tokyo, Japan) with
229 10^5 trials and a random number sampling method (Latin Hypercube Sampling). The basic
230 structure of the procedure is shown in Fig. SB1 (Supplementary Information B). Monte Carlo
231 inputs were those related to the characterization of the exposure scenarios, that is, rates of food
232 and water intake, concentrations in the air, inhalation exposure times, and dermal exposure
233 times. Niizuma et al. (2013) have applied the Monte Carlo method and estimated the probability
234 distributions of TCM exposures via food consumption, inhalation (concentrations in the air and
235 inhalation exposure times), and dermal contact (exposure times) by using exposure
236 concentration data (Itoh and Asami, 2010), nutrition survey data (MHLWJ, 2006), and data for
237 exposure time (NHK-BCRI, 2006; ULRI, 1999). In this study, we basically followed the method
238 of Niizuma et al. (2013) and used the data from these data sources. When data were not available,
239 we predicted data by extrapolation from existing data (details may be found in Supplementary
240 Information B).

241 Beside the inputs via the method of Niizuma et al. (2013), the oral intake rate of drinking
242 water was a random number chosen from a probability distribution function (a Monte Carlo
243 input). The distribution of water consumption rates that we used for the Monte Carlo-simulated
244 inputs is shown in Fig. SB7 (Supplementary Information B). We also considered the variability
245 of the body weights of Japanese adults. Body weight was a random number chosen from the
246 distribution of body weights of Japanese adults (Fig. SB8, Supplementary Information B).

Physiological model parameters (alveolar ventilation rate and exposed body surface area) were determined as a function of body weight according to the following equations (Clewell et al., 2001; Tan et al., 2006a):

$$Q_{alv} = \phi Q = 24 \times {b_w}^{0.75} \quad (6)$$

$$A_{sk} = 286 \times b_w \quad (7)$$

There were weak correlations between body weight and the random values of food and water intake (Fig. SB9, Supplementary Information B). Overall, Monte Carlo inputs were based on data for ordinary Japanese adults. The inputs, therefore, did not take into consideration children and special subpopulations, such as population occupationally exposed to the target compounds.

3. Results and Discussion

3.1 $R_{2/1}$ and $R_{3/1}$ value determination for estimating oral-equivalent potential dose

3.1.1 THMs

The PBPK model simulations for the THMs were conducted for oral doses, inhalation concentrations, and dermal exposure concentrations, and the AUCs were estimated. Substituting the AUCs into Equation (2) and (3) yielded $R_{2/1}$ and $R_{3/1}$ values, respectively. The results of the calculation are shown in Table SB1 (Supplementary Information B). $R_{2/1}$ and $R_{3/1}$ values were independent from oral doses, inhalation concentrations, and dermal exposure concentrations, and therefore $R_{2/1}$ and $R_{3/1}$ values were determined for each compound. Table 3

summarizes the determined $R_{2/1}$ and $R_{3/1}$ values.

That the $R_{2/1}$ and $R_{3/1}$ values of the THMs were all lower than 1 means that inhalation and dermal exposures resulted in a lower burden to the liver than oral exposure did at the same potential dose. If potential exposures were simply used as the relevant dose metric, therefore, the degree of toxicity from inhalation and dermal contact would be somewhat overestimated compared to the toxicity from oral ingestion. The $R_{2/1}$ values were lower for the compounds with higher volatility (lower blood/air partition coefficient, P_{ba}), probably because the inhalation intake calculated using Equation (8) becomes smaller (Chiu and White, 2006; Niizuma et al., 2013).

$$\text{Inhalation intake rate} = C_{art}Q_t - C_{ven}Q_t = Q_{alv}(C_a - C_{art}/P_{ba}), \text{ when } C_{art} > C_{ven} \quad (8)$$

However, the blood/water partition coefficient (P_{bw}) (Table SA1-2) was not strongly related to the $R_{3/1}$ values. Compounds taken in through dermal exposure can be eliminated through inhalation when the compounds are volatile.

Highly volatile compounds (low blood/air partition coefficient, P_{ba}) such as TCM have high rates of elimination according to Equation (9).

$$\text{Rate of elimination} = C_{ven}Q_t - C_{art}Q_t = Q_{alv}\,C_{art}/P_{ba}, \text{ when } C_{ven} > C_{art} \quad (9)$$

Therefore the $R_{3/1}$ values are lower for the compounds with higher volatility. For every compound, the $R_{2/1}$ value for inhalation exposure was similar to the $R_{3/1}$ value for dermal exposure.

3.1.2 HAAs

297 The values of $R_{2/1}$ and $R_{3/1}$ were determined by the same procedure used to estimate the
298 analogous ratios for the THMs (Table SB1, Supplementary Information B and Table 3). The
299 $R_{3/1}$ and $R_{2/1}$ values of TCAA and DCAA were all 1.0, which would be due to the almost none
300 volatilities of TCAA and DCAA and their blood/air partition coefficient (P_{ba}) values are
301 therefore high, as discussed in the previous section.
302
303 *3.1.3 VOCs*
304 The PBPK model was applied to both TCE and its metabolites (DCAA and TCAA) to
305 estimate target tissue doses for the induction of developmental toxicity: the target organ was the
306 placenta, through which TCE and its metabolites pass to the fetus. AUC of TCE and its
307 metabolites in the placenta were calculated for several oral doses, inhalation concentrations,
308 and dermal exposure concentrations of TCE, and the values of $R_{2/1}$ and $R_{3/1}$ were determined
309 by the same procedure used to estimate the analogous ratios for THMs (Table SB1,
310 Supplementary Information B). The values of $R_{2/1}$ and $R_{3/1}$ were greater than 1.0 for TCE and
311 less than 1.0 for the metabolites. Ingested TCE is metabolized during the first pass through the
312 liver, and then it is delivered to the placenta via systemic circulation. However, both inhaled
313 and dermally absorbed doses are delivered directly via systemic circulation and are not modified
314 by first passing through the liver. Therefore, inhaled and dermally absorbed doses are delivered
315 at a higher rate than an ingested dose, the result being that $R_{2/1}$ and $R_{3/1}$ are larger than 1 for
316 TCE. In contrast, because the concentrations of DCAA and TCAA are increased rather than
317 decreased as a result of the passage of TCE through the liver, their $R_{2/1}$ and $R_{3/1}$ values are less
318 than 1. In the following exposure estimations (Section 3.2), the values of $R_{2/1}$ and $R_{3/1}$
319 determined for the metabolites DCAA and TCAA were used for the following exposure
320 assessment of TCE because the metabolites are thought to be responsible for the toxicity
321 (USEPA, 2011b).

The TDI of PCE was determined from administered doses based on the incidence of hepatic cysts (Table 2). We calculated concentrations of both PCE and its metabolite (TCAA) in the venous blood leaving the liver for several PCE oral doses and inhalation and dermal concentrations, and the values of $R_{2/1}$ and $R_{3/1}$ were determined by the same procedure used to calculate the analogous ratios for THMs (Table SB1, Supplementary Information B, Table 3). The $R_{2/1}$ and $R_{3/1}$ values were consistent with the trend obtained for the THMs: the $R_{2/1}$ and $R_{3/1}$ values were lower for the compounds with higher volatility (low blood/air partition coefficient, P_{ba}). The values of $R_{2/1}$ and $R_{3/1}$ of the metabolite TCAA were used in the following exposure assessment of PCE because the hepatotoxic effects of PCE is thought to be due to the metabolite TCAA (USEPA, 2012; WHO, 2003).

3.2 Exposure assessment

The probability distributions of the total oral-equivalent potential dose were calculated for given concentrations in drinking water by the Monte Carlo method. A drinking water concentration that yielded a 95th percentile estimate equal to TDI (95% of estimates ≤ TDI) would be protective for a majority of the population, assuming that the upper 95% confidence limit is a useful indicator of high-end exposure (Nakanishi et al., 2006; Nitta et al., 2003; Nougadère et al., 2011; USEPA, 2000). These concentrations were also calculated for the eight target compounds.

3.2.1 THMs

If drinking water contained the THMs of the JDWQS concentrations, the probability that the daily intake of any one of them would exceed its respective TDI was very low (Fig. SC1, Supplementary Information C). The JDWQS values are therefore protective for the majority

(>95%) of the population, but at the same time the JDWQS values may be somewhat conservative.

A TCM concentration of 140 μg/L yielded a 95th percentile estimate of daily TCM intake equal to the TDI of 12.9 μg/(kg d) (Table 2). In other words, when people drink and use water with a TCM concentration equal to 140 μg/L every day, the 95th percentile of the cumulative distribution of daily TCM intake is 12.9 μg/(kg d). The median is 7.1 μg/(kg d). Figure 1A shows the median and 95th percentile estimates and their breakdown (% ratio to the TDI) with respect to exposure routes. For the median-exposure (the 50^{th} percentile estimate) subpopulation, the intake of TCM via direct consumption of drinking water was 28% of the TDI, and it was 43% for the high-end exposure subpopulation (the 95th percentile estimate). The percentages of 28% and 43% resulted from water intakes of 1.27 and 1.98 L/d, respectively, for a person of a 50-kg body weight, which is the default assumption in determining JDWQS values. If a 50-kg person (default values used in determining the JDWQS values) drinks water containing TCM (140 μg/L) at a rate of 2 L/d, the exposure from this intake would be 5.6 μg/(kg d), which is 43% of the TDI. The difference between the median and high-end exposure was partly due to the difference of water intake, but the difference was primarily caused by the difference of inhalation exposures (Niizuma et al., 2013). Dermal absorption did not contribute much to the total exposure. The reasons of the small contribution are presented elsewhere (Niizuma et al., 2013), but briefly this is due to the differences exposure scenarios, employed skin permeability coefficient values and relevant dose metrics.

In the previous study in which drinking water intake rate was fixed to 2 L/d, the concentration that causes the 95th percentile dose equal to the TDI was 110 μg/L (Niizuma et al., 2013): that is lower than the concentration of 140 μg/L obtained in this study. The lower concentration would reflect that the 2 L/d intake rate is higher than the actual intake rate: for median exposure subpopulations it was 1.27 L/d and even for the high-end exposure subpopulations it was 1.98

L/d.

For BDCM, a concentration of 66 μg/L, which is larger than the JDWQS, yielded a 95th percentile estimate equal to the TDI of 6.1 μg/(kg d). The median estimate was 3.3 μg/(kg d) (Fig. 1B). The contributions from each exposure route were similar to those of TCM.

For DBCM, a concentration of 157 μg/L, which is larger than the JDWQS, yielded a 95th percentile estimate equal to the TDI of 21 μg/(kg d). The median estimate was 8.8 μg/(kg d) (Fig. 1C). That the contribution from inhalation exposure was higher for DBCM than for BDCM and TCM could be due to the larger effect of evaporation of DBCM from water (high b_k (r) value, Table SB2, Supplementary Information B).

A TBM concentration of 203 μg/L, which is larger than the JDWQS, yielded a 95th percentile estimate equal to the TDI of 17.9 μg/(kg d) (Fig. 1D). The median estimate was 9.9 μg/(kg d). That the contribution from inhalation exposure was somewhat lower for TBM than for BDCM and TCM could be due to the lower evaporation rate of TBM: the Henry's law constant and the transfer efficiency of TMB were the lowest among the THMs (Table SB1, Supplementary Information B).

The concentrations of all the THMs that yielded 95th percentile estimates identical to the corresponding TDI were larger than the corresponding JDWQS values. Drinking water containing these THM concentrations at a rate of 2 L/d would result in oral exposure from the drinking water equal to 30–45% of the corresponding TDIs (Table 2). These percentages are higher than the default allocation factor of 20% that is applied in setting the JDWQS.

A comparison with the WHO guideline values (Table 2) revealed that the concentrations associated with the 95th percentile estimates were lower for TCM and very similar for BDCM. For TCM, the 95th percentile estimate (140 μg/L) was about 1/2 of the WHO guideline value (300 μg/L). The TCM WHO guideline value of 300 μg/L would therefore not be applicable to Japan. The WHO value of 300 μg/L was derived by allocating 75% of the TDI to drinking water

(WHO, 2011). However, the WHO guideline also suggests a value lower than 300 μg/L, such as 150 μg/L, for cases where much exposure comes from routes other than ingestion: inhalation of indoor air with a high TCM concentration due largely to volatilization from drinking water and inhalation and dermal exposure during showering or bathing. This scenario applies to Japan, a country where people take showers and bathe frequently (Niizuma et al., 2013). Consequently, we feel that a value lower than 300 μg/L would be reasonable as the JDWQS for TCM.

For the median-exposure (the 50th percentile estimate) subpopulation, indirect consumption of water amounted to 1.16–1.47 Leq/d, which accounted for 22–27% of the TDIs (Fig. 1 and Table 2). For the high-end exposure (the 95th percentile estimate) subpopulation, indirect consumption of water was 2.4–5.1 Leq/d, which accounted for 55–76% of the TDIs. For the high-end exposure populations, maximum acceptable concentration derived by equation (10) for each compound are also listed in Table 2. The concentrations were larger than the corresponding JDWQS and WHO guideline values.

$$C_{\mathrm{M}} = \frac{\mathrm{TDI} \times b_{\mathrm{w}} \times A_{\mathrm{f}}}{I_{\mathrm{direct}} + I_{\mathrm{indirect}}} \qquad (10)$$

The high indirect exposures of THMs were due to evaporation from water. Dermal contact accounted for less than 6% of total exposure, which is lower than the percentages reported previously (Kim et al., 2004; Xu et al., 2002; Yanagibashi, 2010). The reason for the low dermal exposure is discussed by Niizuma et al. (2013). Briefly, our study dealt with internal exposure, whereas the previous studies dealt with potential exposure. The low percentage associated with dermal contact was also due to the difference in exposure scenarios: our study dealt with total daily exposure, whereas the other studies compared inhalation and dermal exposures only during bathing.

Differences in inhalation exposure scenarios made the 95th percentile estimate much larger

than the median estimate. The large amount of exposure from inhalation was caused mainly by the high THM concentrations in the inhaled air and not by longer exposure time (Fig. SC2, Supplementary Information C) (Niizuma et al., 2013).

3.2.2 HAAs

For DCAA and TCAA, the concentrations that resulted in 95th percentile estimates equal to the TDI were 140 and 78 μg/L, respectively (Fig. 2 and Table 2). These values were both larger than the corresponding JDWQS and WHO guideline values. The JDWQS value for TCAA is based on its TDI, but our results (Fig. SC3, Supplementary Information C) indicated that the probability that the total daily intake of TCAA might exceed the TDI was very low even if drinking water contained TCAA at its JDWQS concentration. Therefore, the JDWQS value for TCAA is protective for the majority (>95%) of the population, but it may be conservative. For DCAA, in contrast, the JDWQS value of 30 μg/L was derived from a virtually safe dose (VSD) for a water intake of 2-L/d at a risk of 10^{-5} in the unit cancer risk approach because this value was lower than the value of 140 μg/L, which was derived from the TDI of 12.5 μg/(kg d) and an allocation factor of 10%. Our result clearly indicates that the JDWQS value of 30 μg/L, which was derived with the unit cancer risk approach, provides a margin of safety in terms of non-cancer assessment on the TDI.

When one drinks water containing DCAA (140 μg/L) and TCAA (78 μg/L) at a rate of 2 L/d, the oral exposure from the drinking water accounts for 45–52% of the respective TDIs (Fig. 2). These percentages are higher than the default value of 20% that is applied in setting the JDWQS. The contributions from dermal and inhalation exposures were very low. Similar insignificant contributions from dermal and inhalation exposures can be predicted from skin permeability coefficients and volatilities (Krishnan and Carrier, 2008). It should be noted that for high-end exposure, 40–54% of the total exposures was accounted for by food intake, whereas food intake

accounted for 24–31% of total exposure for the median-exposure group. Cooking food with water raised the HAA concentrations and then the exposure via food intake, which originated from the cooking water. Therefore, indirect exposure via food was the major exposure route for the HAAs, which are not volatile compounds. In contrast, for the THMs, which are volatile compounds, indirect exposure via inhalation was the major exposure route, as described in subsection 3.2.1. Indirect water intakes for DCAA and TCAA exposure were 1.4 and 1.0 Leq/d, respectively, for the median-exposure subpopulation; they were 2.4 and 1.6 Leq/d, respectively, for the high-end exposure subpopulation. These values are not small, even when compared with those for the THMs. The difference in exposures via food intake made the 95th percentile estimate much larger than the median estimate (Fig. 2). Per-capita water and food consumption were large for people with large body weights, but consumption per unit body weight was somewhat larger for people with relatively low body weights (Matsui, 2013). Therefore, a relatively large rate of food and water intake per unit body weight for the low-body-weight subpopulation might have been a major cause of their high exposure. Actually, the body weights of the high-exposure subpopulation were somewhat smaller than those of the median-exposure subpopulation (Fig. SC4, Supplementary Information C). However, exposure distributions did not vary much as a function of body weight (Fig. SC5, Supplementary Information C). Persons in the low-body-weight subpopulation would not be vulnerable, despite their relatively large rate of food and water intake per unit body weight.

DBPs, including THMs and HAAs, are usually not detected in high concentrations in uncooked foods and natural air (Itoh and Asami, 2010). However, allocation factors are not assigned large percentage values for drinking water in Japan, partly because of consideration of the contributions of indirect exposure, possibly via inhalation. A single, small default value of 20%, which is allocated to ingestion of drinking water at a rate of 2 L/d, is used as the allocation factor of DBPs (both THMs and HAAs), although the physical and chemical properties that

affect volatility are very different for THMs and HAAs. HAAs are not volatile compounds, whereas THMs are volatile. Therefore, we had anticipated that the contributions of water intakes derived in this study would have been very different for THMs and HAAs. However, the contributions derived in this study were not very different: they were 30–45% of the TDIs for THMs and 45–52% for HAAs. Ingestion of food was a major indirect route for HAAs, whereas inhalation was a major indirect route for THMs due to volatilization from drinking water. If the smallest percentage derived in this study, 30%, is adopted as the overall allocation factor for DBPs to ensure that the policy is protective, then the current default allocation factor of 20%, which is not so different from that value, is consistent with the goal of protection and is supported by the results of this study.

3.2.3 VOCs

Figure 3A shows the probability distribution of total oral-equivalent potential dose when the TCE concentration in water is 10 μg/L (the JDWQS value). Under this condition, about 20% of the population exceeds the TDI of 1.46 μg/(kg d). The concentration of TCE that resulted in a 95th percentile estimate equal to the TDI of 1.46 μg/(kg d) (5% of the population exceeds the TDI) was 6.55 μg/L (Table 2, Figs. 3A and 4A).

In the derivation of the current JDWQS value, 70% of the TDI was allocated to ingestion of drinking water at a rate of 5 L/d, which is 2 L/d for direct intake plus 3 Leq/d for indirect intake via volatilization from water based on Equation (10). Our calculations indicate that indirect intake via inhalation of air containing TCE volatilized from water is the major source of exposure, and indirect intake is much larger than direct intake from drinking water (Fig. 4A). The estimated indirect water intake rates were mostly larger than 3 Leq/d, which is applied in the derivation of the current JDWQS value. They were 3.1 Leq/d for the median-exposure subpopulation (the 50th percentile estimate) and 9.1 Leq/d for the high-end exposure (the 95th

497 percentile estimate) subpopulation. These values were also much larger than those of the THMs.
498 It should be due to the high evaporation rate of TCE. The Henry's law constant for TCE is more
499 than two times that of the TMHs, and the transfer efficiency of TCE was therefore more than
500 two times that of the THMs (Table SB1 of Supplementary Information B). The observed TCE
501 concentrations in air and water in bathrooms, however, indicate that the intensity of TCE
502 evaporation is around 3.75 times that of TCM (Fig. SB3 of Supplementary Information B), the
503 suggestion being that the indirect water intake rate through evaporation should be much higher
504 for TCE than the THMs. For the high-end exposure subpopulation, the indirect water intake
505 rate was very high, 9.1 Leq/d. Most of the indirect water intake was caused by inhalation in the
506 bathroom. High TCE concentrations in bathroom air would produce a high-end exposure
507 subpopulation (the 95th percentile estimate). Such high concentrations could be caused by low
508 ventilation rates in the rooms and/or any activities that cause high rates of TCE evaporation
509 from water, as suggested by Niizuma et al. (2013).

510 It should also be noted that total oral-equivalent potential dose values and Leq/d values are
511 changed depending on model parameter and input values. The large contribution of inhalation
512 to total exposure indicates that the model parameter and input for inhalation exposure [$R_{2/1}$
513 and $\overline{C_a}$ in equation (1)] influence the results of total oral-equivalent potential dose. The high
514 TCE evaporation rate and long bathing/showering time raise the daily-average concentration in
515 inhaled air ($\overline{C_a}$), as discussed earlier. In the simulation which produced the results of Figs. 3A
516 and 4A, the $R_{2/1}$ value of the TCE' metabolites was applied because of the general consideration
517 that the TCE toxicity reside in its metabolites (USEPA, 2011b). When the $R_{2/1}$ values for the
518 TCE, which is 4 times as large as those of the metabolites, was applied in the simulations, the
519 contribution of inhalation exposure becomes higher: the indirect intake via inhalation increased
520 by about 4 times (e.g., from 3.1 to 13.5 L/d for the median-exposure subpopulation (compare
521 Fig. 4A and Fig SC6 of Supplementary Information C). The concentration of TCE that resulted

in a 95th percentile estimate equal to the TDI of 1.46 μg/(kg d) became smaller: it was 1.6 μg/L (Fig SC7 of Supplementary Information C). Therefore, the outcome of the simulation is sensitive to the $R_{2/1}$ value as well as exposure scenarios for inhalation. The value of $R_{2/1}$ is determined depending on the mode of action for toxicity, while the exposure scenarios are dependent on local conditions including long-time showering and bathing and/or in poorly ventilated buildings.

Figure 3B and 4B show the results for PCE. The concentration that resulted in the 95th percentile estimate equaling the WHO TDI of 14 μg/(kg d) was 22 μg/L (Table 2), roughly twice the JDWQS value of 10 μg/L. The JDWQS value was derived from a VSD for a water intake of 2-L/d at a risk of 10^{-5} in the unit cancer risk approach because the value of 10 μg/L was lower and on the safer side than the value of 40 μg/L, which was derived from the TDI of 14 μg/(kg d) and an allocation factor of 10%. Our results clearly indicate that the JDWQS of 10 μg/L, which was derived from the VSD in the unit cancer risk approach, includes a margin of safety in terms of the non-cancer assessment on the TDI. It should also be noted that the indirect intake of PCE was very high: it was 9 Leq/d for the median-exposure sub-population. This is due to the high evaporation rate of PCE. The intensity of PCE evaporation was around 12 times that of TCM (Fig. SB5 of Supplementary Information B).

4. Summary

For THMs and TCAA, concentrations that caused the 95th percentile estimate to equal the corresponding TDI were higher than the corresponding JDWQS values, which are based on TDI values with an allocation factor of 20%. For DCAA and PCE, the JDWQS values of 30 and 10 μg/L, respectively, which are derived from the VSD for a water intake of 2 L/d and a risk of 10^{-5} in the unit cancer risk approach, provided a margin of safety in terms of non-cancer

risk assessment: the probabilities that the intakes would exceed the TDIs were below 5%. When the TCE concentration in water equals the JDWQS value of 10 μg/L, we estimated that the TCE intake of about 20% of the population would exceed the TDI. The high TCE exposure of the population was due to the high TCE concentrations in bathroom air; it had little to do with other characteristics, such as direct intake from water and food and low body weight. The TCE concentration that causes the 95th percentile estimate to equal the TDI was 6.55 μg/L, which is lower than the JDWQS value. The contributions of indirect water intake for HAAs were not very different from those derived for THMs. Ingestion of food, however, was a major indirect route of exposure for HAAs, whereas inhalation was a major source of exposure to THMs because of volatilization from drinking water. For the median-exposure population, indirect water intake of the eight compounds ranged from 1 to 9 Leq/d. The indirect water intake rate through evaporation was much higher for TCE and PCE than TCM. The intensities of TCE and PCE evaporations in bathroom was higher than those estimated from the Henry's law constant the transfer efficiency.

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Conflict of Interest statement

The authors declare that there are no conflicts of interest.

572 **Abbreviations**

Symbols	Definition
A_D	Daily oral intake (mg/d)
A_{oral}	Oral intake rate (an input of PBPK model simulation, mg/d)
A_f	Allocation factor (%)
A_{sk}	Body surface area (cm^2)
b_w	Body weight (kg)
$C_{inhalation}$	Concentration in inhaled air (an input of PBPK model simulation, mg/L)
$\overline{C_a}$	Daily-average concentration in inhaled air (mg/L)
C_{alv}	Concentration in alveolar air (mg/L)
C_{art}	Concentration in arterial blood (mg/L)
C_{dermal}	Concentration in water for dermal adsorption (an input of PBPK model simulation, mg/L)
$\overline{C_d}$	Daily-average concentration in water for dermal adsorption (mg/L)
C_M	Maximum acceptable concentration (mg/L)
C_{ven}	Concentration in mixed venous blood (mg/L)
D_T	Total oral-equivalent potential dose [mg/(kg-body d)]
K_p	Effective skin permeability coefficient (cm/d)
I_{direct}	Direct daily drinking water consumption (L/d)
$I_{indirect}$	Indirect daily drinking water consumption (Leq/d)
P_{ba}	Blood/air partition coefficient (dimensionless)
Q	Breathing rate (L/d)
Q_{alv}	Alveolar ventilation rate (L/d)
Q_t	Cardiac output (L/d)
t_{oral}	Oral exposure time (an input of PBPK model simulation, d)
$t_{inhalation}$	Inhalation exposure time (an input of PBPK model simulation, d)
t_{dermal}	Dermal exposure time (an input of PBPK model simulation, d)
TDI	Tolerable daily intake [mg/(kg-body d)]
$R_{2/1}$	Relative availability (dimensionless), which is the same as the product of $\alpha_{2/1}$ and $\beta_{2/1}$ of Niizuma et al. (2013)
$R_{3/1}$	Relative availability (dimensionless), which is the same as the product of $\alpha_{3/1}$ and $\beta_{3/1}$ of Niizuma et al. (2013)
ϕ	Ratio of alveolar ventilation rate to breathing rate (dimensionless)

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Figure captions

Fig. 1. Total oral-equivalent potential doses of TCM, BDCM, DBCM, and TBM (Panels A, B, C, and D, respectively) when the 95th percentile estimates were equal to the corresponding TDIs. The second and third bars show the median (50th percentile) and the 95th percentile estimates, respectively. The TCM, BDCM, DBCM, and TBM concentrations in drinking water were equal to 140, 66, 157, and 203 μg/L, respectively.

Fig. 2. Total oral-equivalent potential doses of DCAA and TCAA (Panels A and B, respectively) when the 95th percentile estimates were equal to the corresponding TDIs. The second and third bars show the median (50th percentile) and the 95th percentile estimates, respectively. The DCAA and TCAA concentrations in drinking water were equal to 140 and 78 μg/L, respectively.

Fig. 3. The probability density functions of the total oral-equivalent potential dose of TCE and PCE (Panels A and B, respectively) when concentration in drinking water (C_W) are 1, 2, 5, 6.55 and 10 μg/L for TCE and 5, 10, 20 and 50 μg/L for PCE. The red lines indicates TDIs of TCE and PCE.

Fig. 4. Total oral-equivalent potential doses of TCE and PCE (Panels A and B, respectively) and their breakdown products when the 95th percentile estimates were equal to the corresponding TDIs. The second and third bars shows the median (50th percentile) and the 95th percentile estimates, respectively. The TCE and PCE concentrations in drinking water were equal to 6.55 and 22 μg/L, respectively.

Table captions

Table 1. Target compounds

Table 2. WHO Drinking Water Quality Guideline values, JDWQS values, and the values obtained in this study.

Table 3. Values of $R_{2/1}$ and $R_{3/1}$ used in the Monte-Carlo simulations.

Table 1 Target compounds

Disinfection by-products (DBPs)	Trihalomethens (THMs)	Chloroform or Trichloromethane (TCM)
		Bromodichloromethane (BDCM)
		Dibromochloromethane (DBCM)
		Bromoform or Ttribromomethane (TBM)
	Haloacetic acids (HAAs)	Dichloroacetic acid (DCAA)
		Trichloroacetic acid (TCAA)
Volatile organic carbons (VOC)		Trichloroethene or Trichloroethylene (TCE)
		Tetrachloroethene, Tetrachloroethylene or Perchloroethylene (PCE)

Table 2 WHO Drinking Water Quality Guideline values, JDWQS values, and the values obtained in this study.

		Japanese Drinking Water Quality Standard					WHO Drinking Water Quality Guideline	95th percentile dose estimate equals to TDI (95% of D_T estimates ≤ TDI)		High-end exposure population			Median-exposure population	
		DWQS value	Endo point organ	Base of the DWQS value				Concentration	Contribution of direct water intake (% ratio to TDI) when a 50-kg person drinks water of the left concentration at a rate of 2 L/d	Direct water intake (% to total intake)	Indirect water intake (% to total intake)	Concentration by equation (10) with the assumption of 80% allocation and 50-kg body weight	Direct water intake (% to total intake)	Indirect water intake (% to total intake)
THMs	TCM	60 μg/L	Liver	TDI＝12.9 μg/(kg day) [A]	Allocation factor = 20 %	2 L/day	300 μg/L	140 μg/L	43 %	1.98 L/day (43 %)	2.61 L/day (56 %)	112 μg/L	1.27 L/day (50 %)	1.23 L/day (49 %)
	BDCM	30 μg/L	Liver	TDI＝6.1 μg/(kg day) [B]	Allocation factor = 20 %	2 L/day	60 μg/L	66 μg/L	43 %	1.93 L/day (42 %)	2.69 L/day (58 %)	53 μg/L	1.29 L/day (52 %)	1.16 L/day (47 %)
	DBCM	100 μg/L	Liver	TDI＝21.0 μg/(kg day) [C]	Allocation factor = 20 %	2 L/day	100 μg/L	157 μg/L	30 %	1.60 L/day (24 %)	5.10 L/day (76 %)	125 μg/L	1.35 L/day (48 %)	1.47 L/day (52 %)
	TBM	90 μg/L	Liver	TDI＝17.9 μg/(kg day) [D]	Allocation factor = 20 %	2 L/day	100 μg/L	203 μg/L	45 %	2.00 L/day (45 %)	2.41 L/day (55 %)	162 μg/L	1.25 L/day (51 %)	1.18 L/day (49 %)
HAAs	DCAA	30 μg/L	Liver	Cancer slope factor = 7.8×10^{-3} $[mg/(kg\ day)]^{-1}$	VSD at 10^{-5} risk = 1.3 μg/(kg day) [E]	2 L/day	50 μg/L							
			Liver	TDI＝12.5 μg/(kg day) [X]				140 μg/L	45 %	1.97 L/day (44 %)	2.43 L/day (55 %)	113 μg/L	1.25 L/day (46 %)	1.42 L/day (53 %)
	TCAA	30 μg/L	Liver	TDI＝6.0 μg/(kg day) [F]	Allocation factor = 20 %	2 L/day	200 μg/L	78 μg/L	52 %	2.12 L/day (55 %)	1.60 L/day (41 %)	65 μg/L	1.23 L/day (53 %)	0.98 L/day (43 %)
VOCs	TCE		Liver	Cancer slope factor = 8.3×10^{-3} $[mg/(kg\ day)]^{-1}$	VSD at 10^{-5} risk = 1.2 μg/(kg day) [G]									
		10 μg/L	Fetal heart	TDI = 1.46 μg/(kg day) [Y]	Allocation factor = 70 %	5 L/day	20 μg/L	6.55 μg/L	18 %	1.63 L/day (15 %)	9.14 L/day (82 %)	5.4 μg/L	1.50 L/day (31 %)	3.05 L/day (62 %)
	PCE	10 μg/L	Liver	Cancer slope factor = 0.025 $[mg/(kg\ day)]^{-1}$	VSD at 10^{-5} risk = 0.4 μg/(kg day) [H]	2 L/day								
			Liver	TDI = 14 μg/(kg day) [Z]			40 μg/L	22 μg/L	6.4 %	1.35 L/day (4 %)	29.7 L/day (95 %)	18 μg/L	1.35 L/day (13 %)	9.00 L/day (86 %)

A: Heywood et al. 1979
B: Aida et al. 1992
C: U.S. Department of Health & Human Services 1985
D U.S. Department of Health & Human Services 1989
E: DeAngelo et al. 1999
F: DeAngelo et al. 2008
G: NCI (National Cancer Institute) 1976
H: NCI (National Cancer Institute) 1977
X: CICMANEC et al. 1991
Y: FSC 2010
Z: WHO 2011

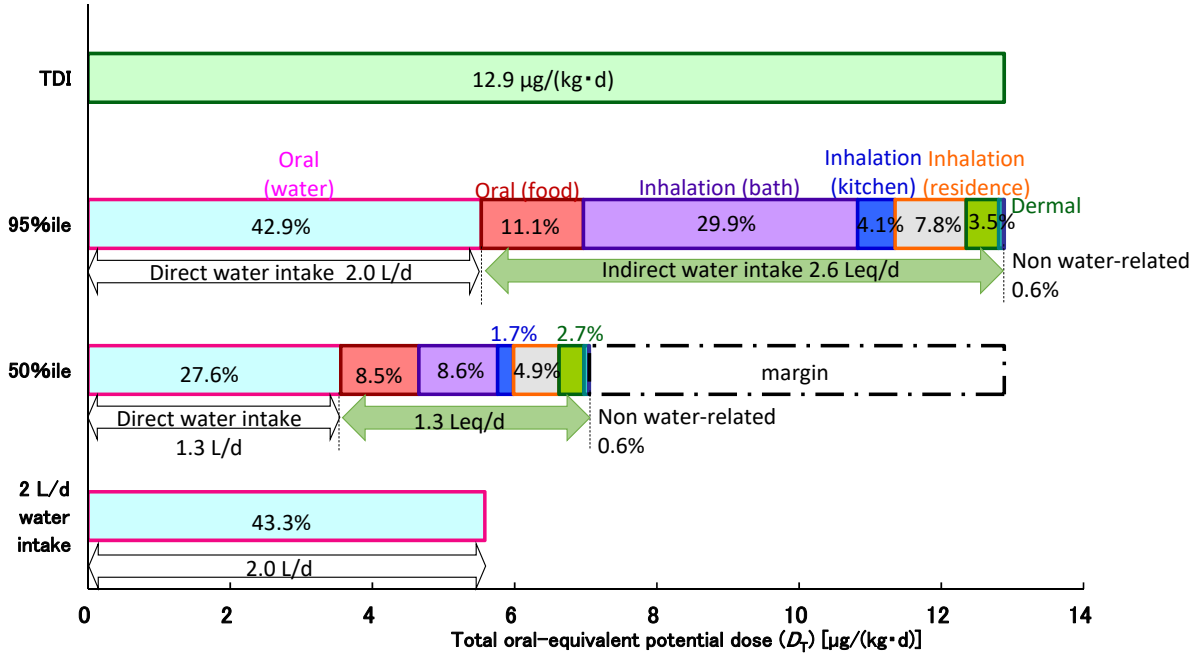
Table 3 Values of $R_{2/1}$ and $R_{3/1}$ used in the Monte-Carlo simulations.

Exposed substance	Endpoint (AUC calculation)	Target substance	$R_{2/1}$	$R_{3/1}$
			dimensionless	dimensionless
TCM	Liver (metabolic rate)	TCM	0.549	0.542
BDCM	Liver (metabolic rate)	BDCM	0.802	0.791
DBCM	Liver (metabolic rate)	DBCM	0.888	0.883
TBM	Liver (metabolic rate)	TBM	0.939	0.940
DCAA	Liver (plasma concentration)	DCAA	1.00	1.00
TCAA	Liver (plasma concentration)	TCAA	1.00	1.00
TCE	Placenta (plasma concentration)	TCAA/DCAA (metabolite) *	0.560	0.654
PCE	Liver (plasma concentration)	TCA (metabolite)	0.672	0.677

* The TCAA and DCAA values were averaged although their differences was small.

Figure 1 (Panels A and B)

Panel A (TCM)



Panel B (BDCM)

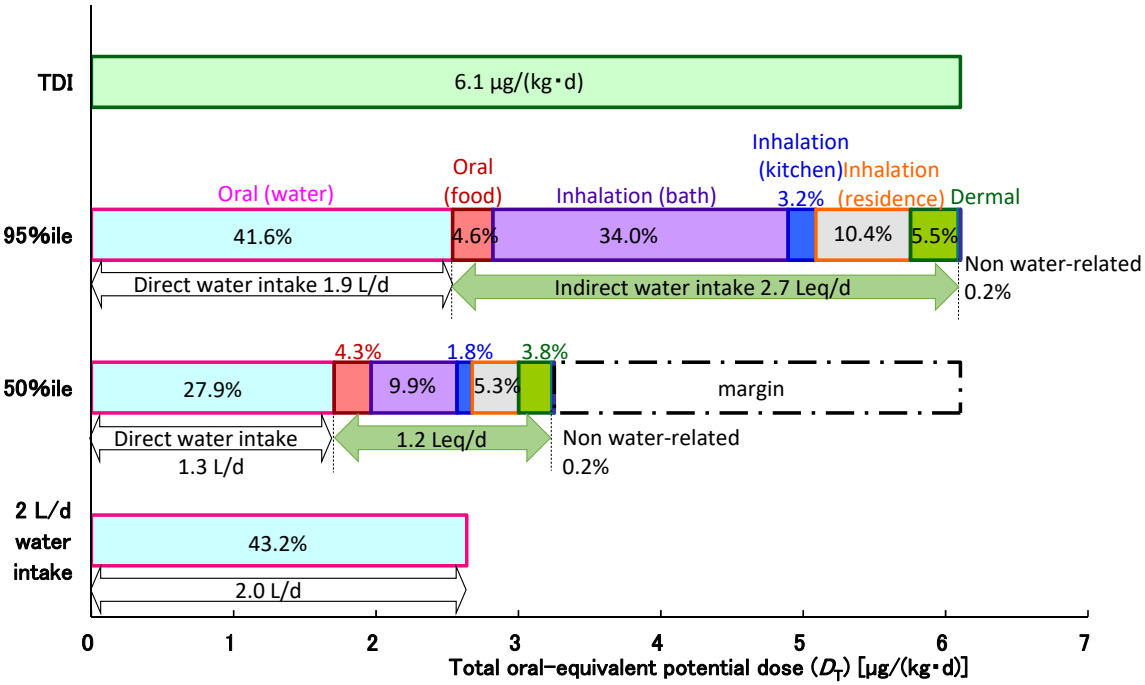
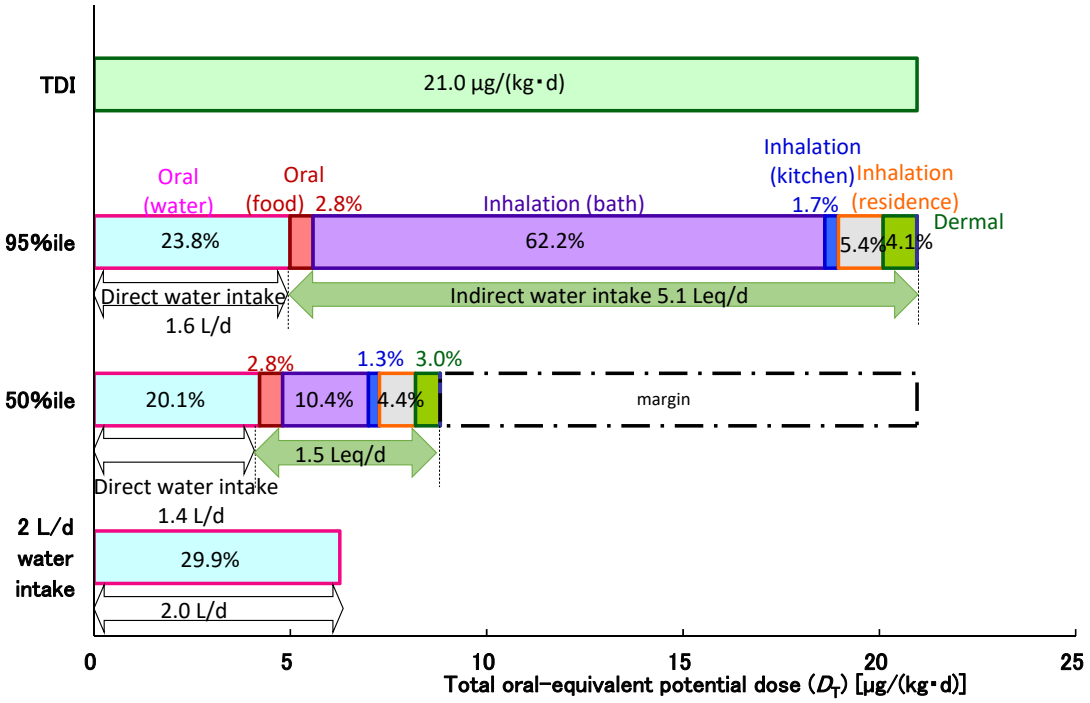


Figure 1 (Panels C and D)

Panel C (DBCM)



Panel D (TBM)

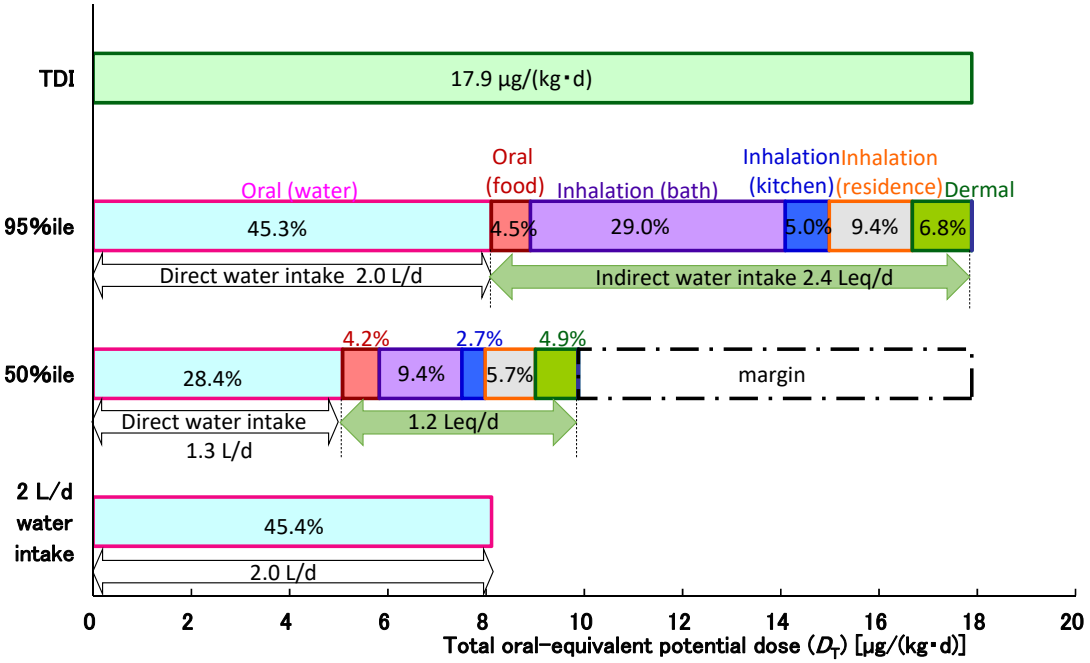
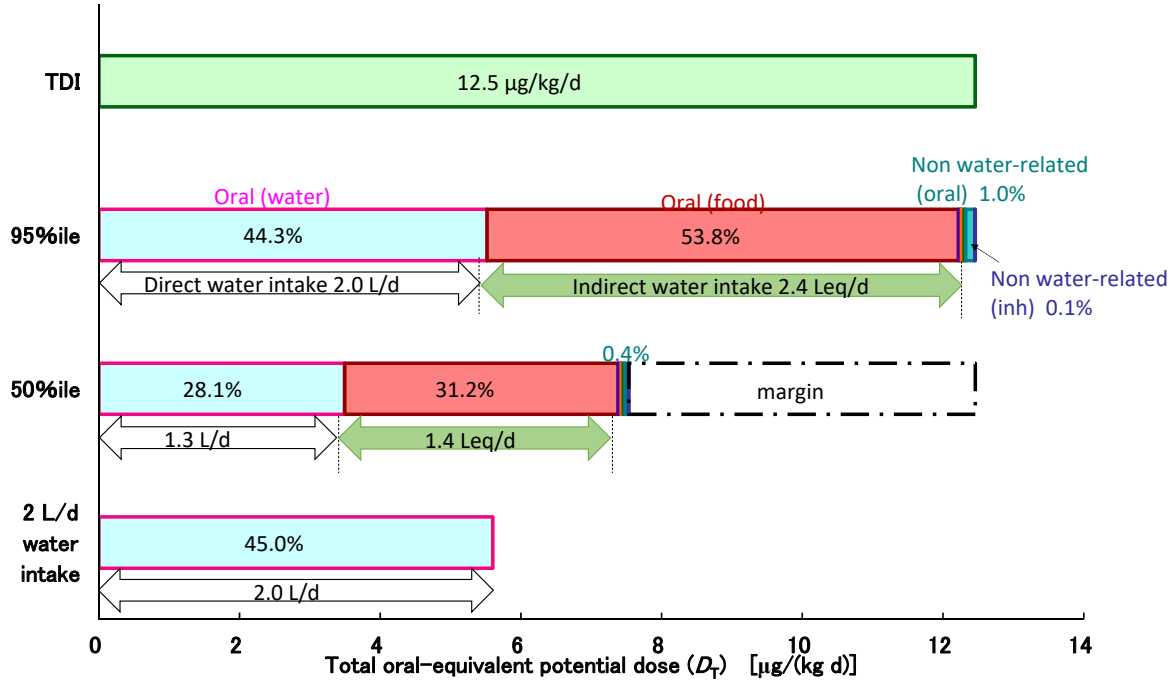


Figure 2 (Panels A and B)

Panel A (DCAA)



Panel B (TCAA)

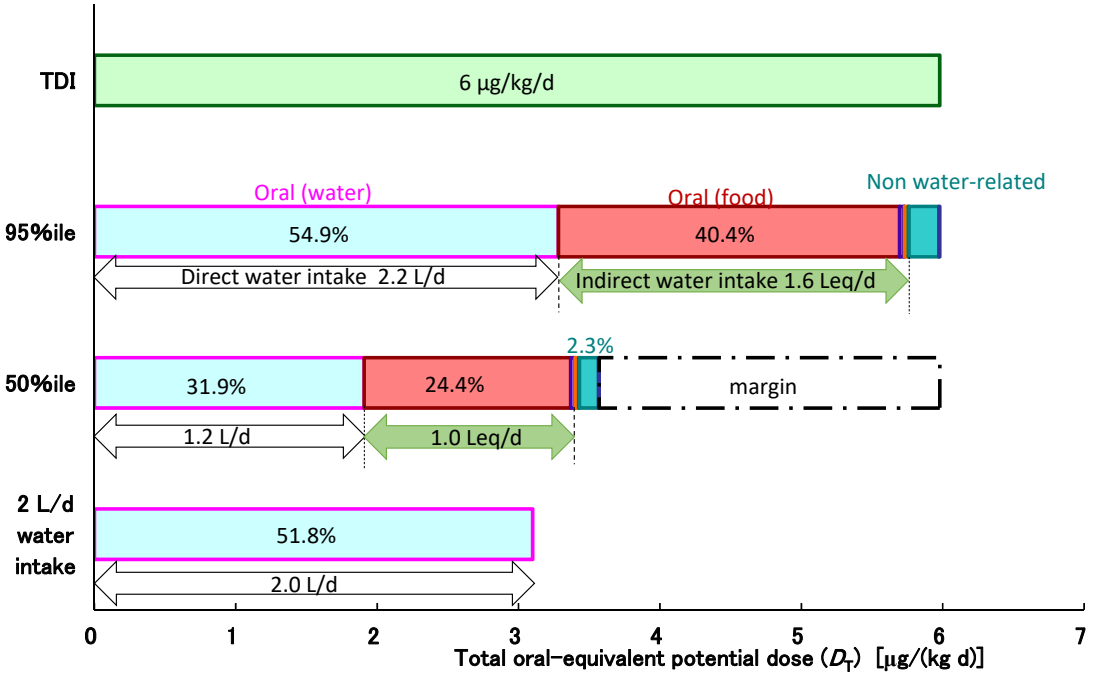
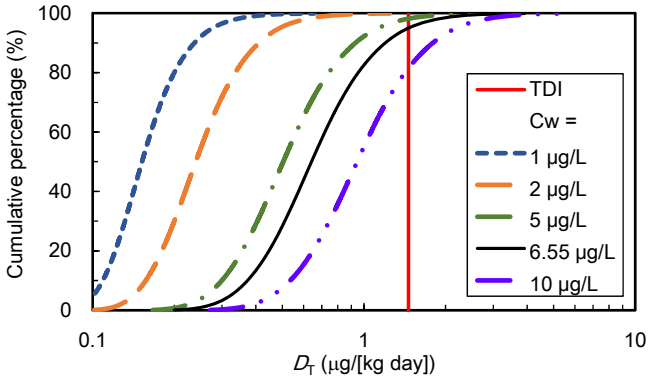


Figure 3 (Panels A and B)

Panel A (TCE)



Panel B (PCE)

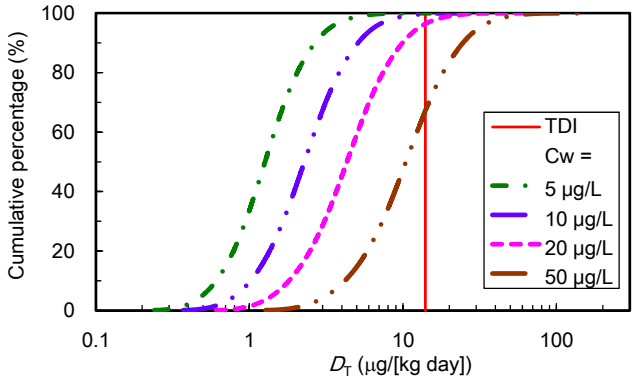
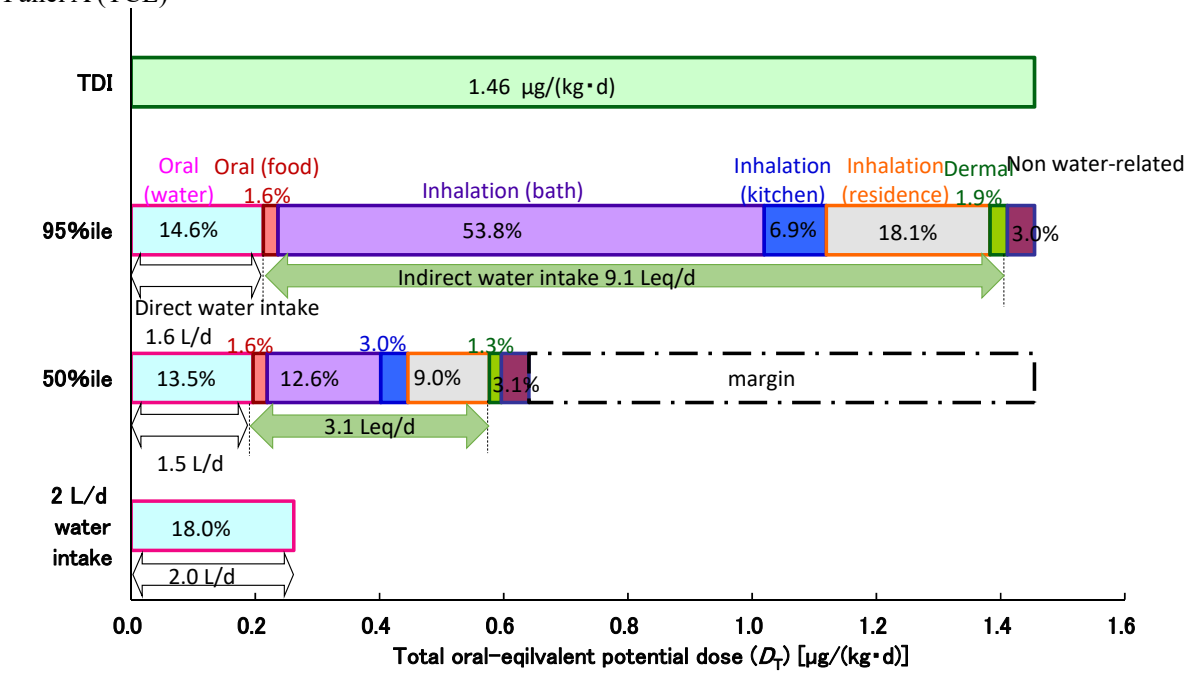
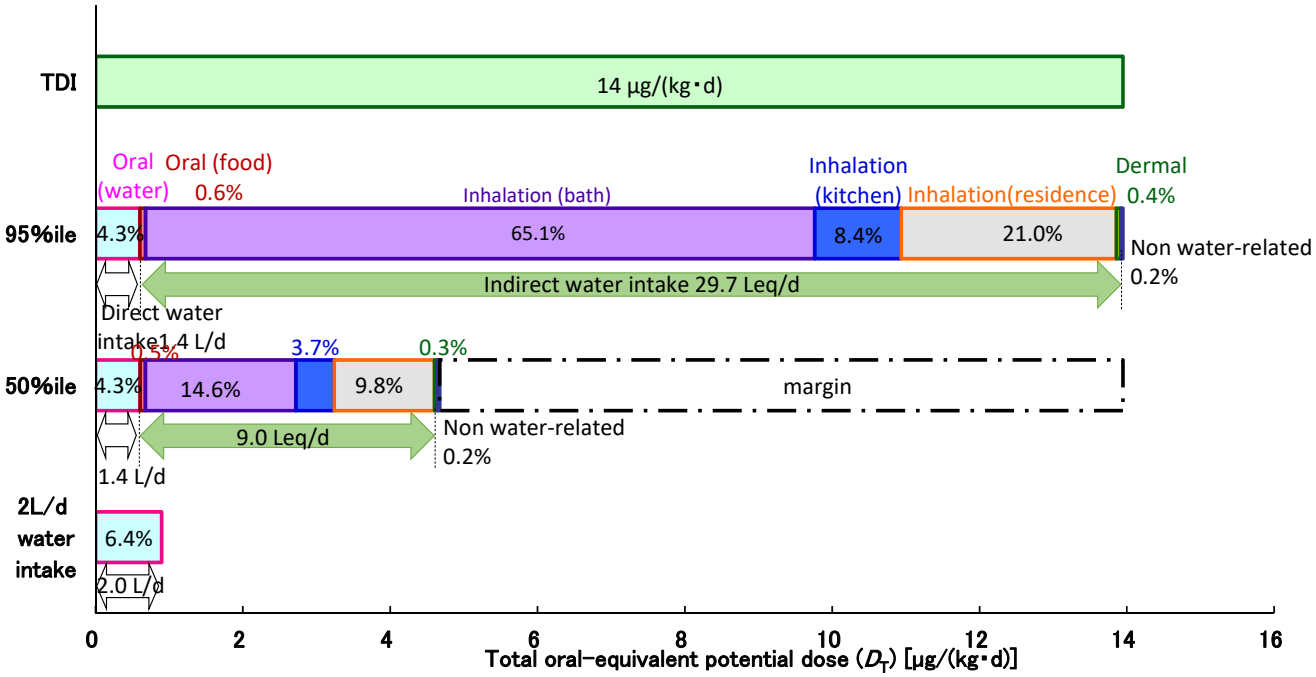


Figure 4 (Panels A and B)

Panel A (TCE)



Panel B (PCE)



Supplementary Information A

Monte-Carlo and multi-exposure assessment for the derivation of criteria for disinfection byproducts and volatile organic compounds in drinking water: allocation factors and liter-equivalents per day

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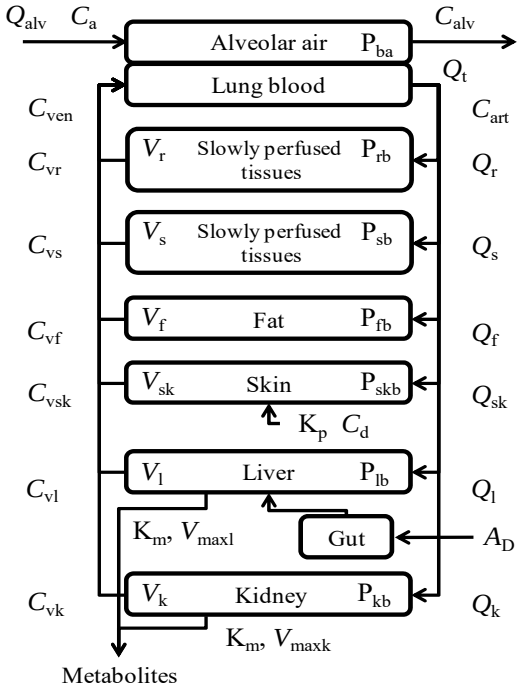

Fig. SA1. Human PBPK model for THMs

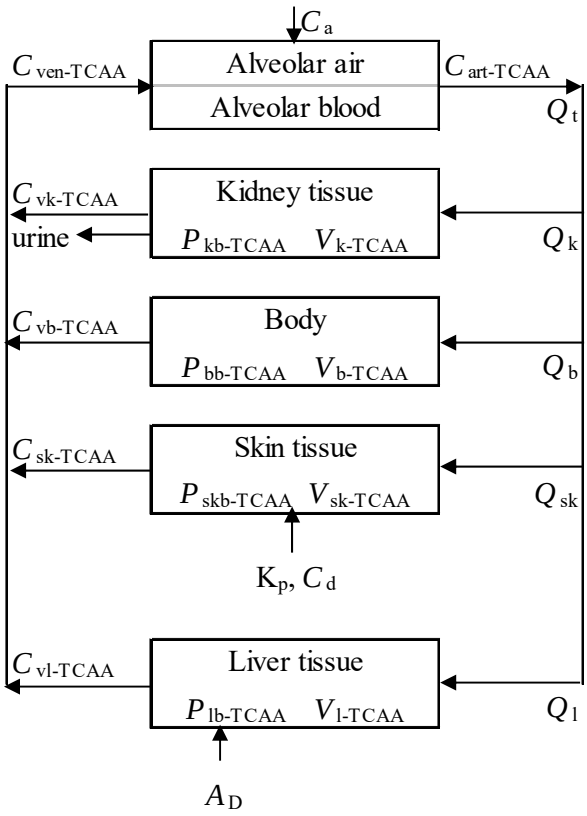

Fig. SA2. Human PBPK model for TCAA

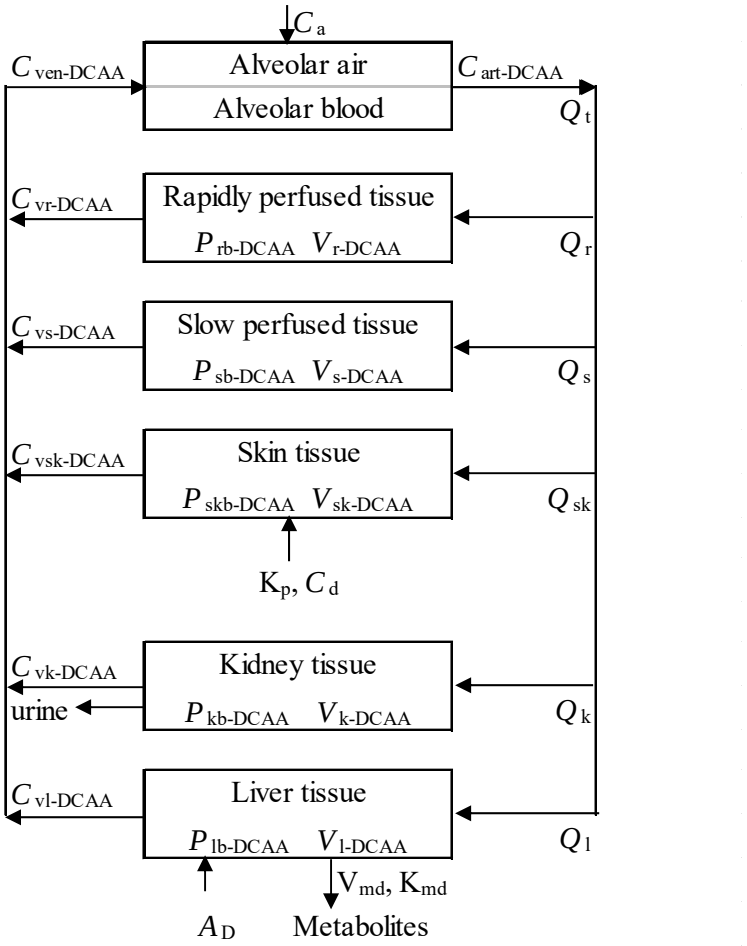

Fig. SA3. Human PBPK model for DCAA

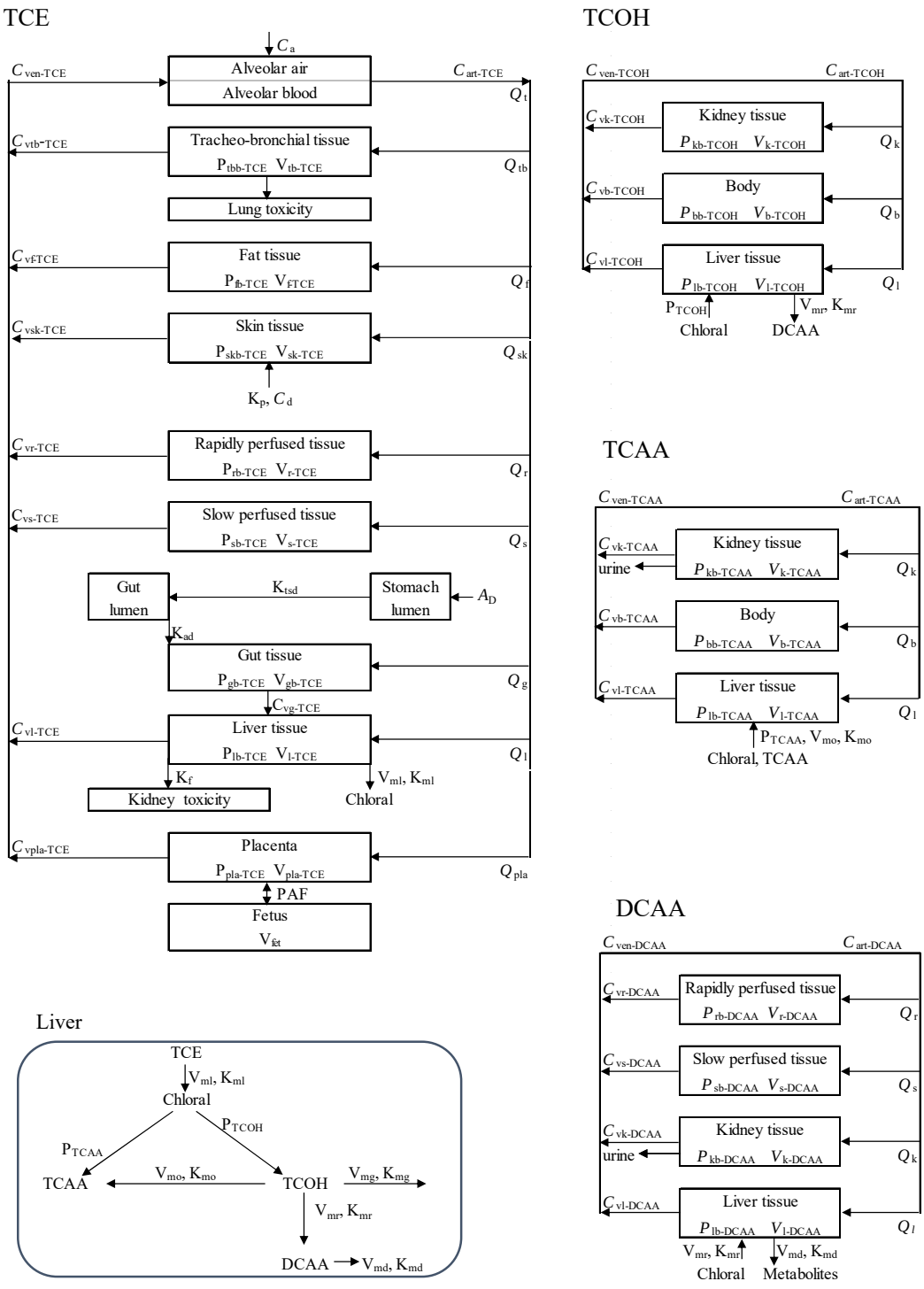

Fig. SA4. Human PBPK model for TCE and its metabolites (TCOH, TCAA, and DCAA) in females

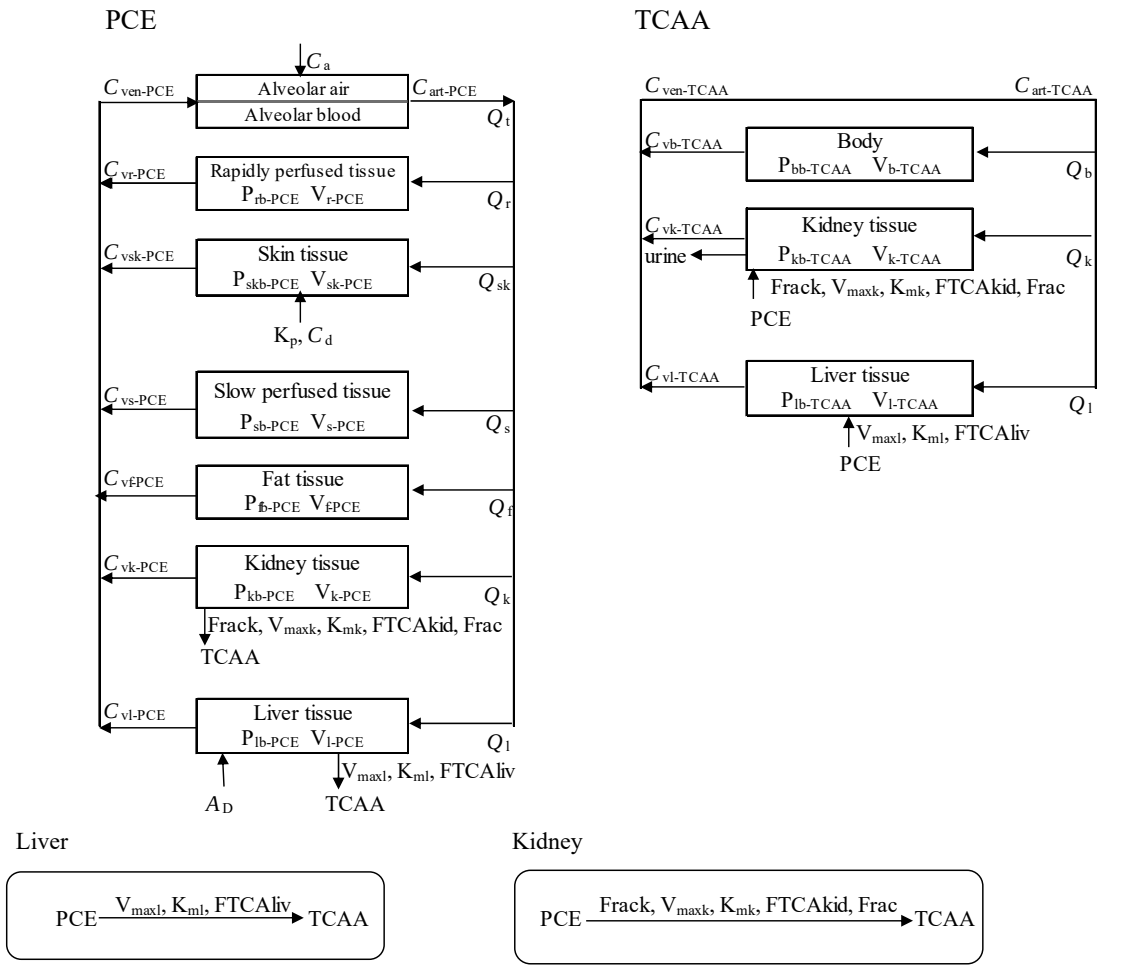

Fig. SA5. Human PBPK model for PCE and its metabolite (TCAA).

Table SA1-1.

Values of the physiological parameters for the THMs

		Parameter (unit)		Value
Body weight		b_w	(kg)	70[b]
Tissue volume (assume unit density)[a]	Rapidly perfused	V_r	(L)	3.77[a]
	Slowly perfused	V_s	(L)	39.3[a]
	Fat	V_f	(L)	15.0[a]
	Skin	V_{sk}	(L)	3.57[a]
	Liver	V_l	(L)	1.80[a]
	Kidney	V_k	(L)	0.308[a]
Alveolar ventilation rate		Q_{alv}	(L/d)	13940[a]
Breathing rate		Q	(L/d)	19110[c]
Ratio of alveolar ventilation rate to breathing rate		ϕ	(dimensionless)	0.729
Cardiac output		Q_t	(L/d)	9583[a]
Blood flow	Rapidly perfused	Q_r	(L/d)	2434[a]
	Slowly perfused	Q_s	(L/d)	1629[a]
	Fat	Q_f	(L/d)	479[a]
	Skin	Q_{sk}	(L/d)	824[a]
	Liver	Q_l	(L/d)	2396[a]
	Kidney	Q_k	(L/d)	1821[a]
Body surface area exposed		A_{sk}	(cm^2)	20020[a]

[a] Tan et al. (2006)

[b] Environment Canada and Health Canada (2001)

[c] USEPA (2011)

[d] $\phi = Q_{alv}/Q$

Table SA1-2

Chemical-specific parameter values for the THMs [a]

		Parameter (unit)	THMs			
			TCM	BDCM	DBCM	TBM
Partition coefficients	Blood/air	P_{ba} (dimensionless)	7.43	26.6	49.2	102.3
	Rapidly perfused/blood	P_{rb} (dimensionless)	2.29	1.15	2.56	2.06
	Slowly perfused/blood	P_{sb} (dimensionless)	1.62	0.47	1.13	1.13
	Fat/blood	P_{fb} (dimensionless)	37.69	19.77	38.96	40.36
	Skin/blood	P_{skb} (dimensionless)	1.62	1.05	1.15	1.17
	Skin/water	P_{skw} (dimensionless)	3.85	4.04	4.28	4.57
	Blood/water	P_{bw} (dimensionless)	2.38	3.85	3.72	3.91
	Liver/blood	P_{lb} (dimensionless)	2.29	1.15	2.56	2.06
	Kidney/blood	P_{kb} (dimensionless)	1.48	1.24	2.56	1.70
Maximum reaction rate	Liver	V_{maxl} (mg/d)	7374	176	268	203
	Kidney	V_{maxk} (mg/d)	41.79	1.00	0	0
Michaelis constant	Liver	K_{ml} (mg/L)	0.448	0.302	0.72	0.42
	Kidney	K_{mk} (mg/L)	0.448	0.302	0	0
Effective skin permeability coefficient		K_p (cm/d)	1.20	1.25	0.54	0.26

[a] Tan et al. (2006)

Table SA2-1

Physiological parameter values for TCAA

		Parameter (unit)		Value
Body weight		b_w	(kg)	70[a]
Tissue volume (assume unit density)[a]	Body	V_b	(L)	53.1[a]
	Lung	V_{lung}	(L)	0.84[a]
	Skin	V_{sk}	(L)	2.45[b]
	Liver	V_l	(L)	1.44[a]
	Kidney	V_k	(L)	0.24[a]
Alveolar ventilation rate		Q_{alv}	(L/d)	13940[a]
Breathing rate		Q	(L/d)	19110[c]
Ratio of alveolar ventilation rate to breathing rate		ϕ	(dimensionless)	0.729[d]
Cardiac output		Q_t	(L/d)	9583[a]
Blood flow	Body	Q_b	(L/d)	5871[a]
	Skin	Q_{sk}	(L/d)	556[b]
	Liver	Q_l	(L/d)	1782[a]
	Kidney	Q_k	(L/d)	1374[a]
Body surface area exposed		A_{sk}	(cm^2)	20020[e]
Urinary excretion		K_{utc}	(/day)	0.552

[a] Fisher et al. (1998)

[b] Poet et al. (2000)

[c] USEPA (2011)

[d] $\phi = Q_{alv}/Q$

[e] Tan et al. (2006)

Table SA2-2

Chemical-specific parameter values for TCAA

		Parameter(unit)	Value
Partition coefficients	Blood/air	P_{ba} (dimensionless)	2.00×10^{7} [f]
	Body/blood	P_{bb} (dimensionless)	0.52 [a]
	Skin/blood	P_{skb} (dimensionless)	0.52 [a]
	Skin/water	P_{skw} (dimensionless)	5.76 [b]
	Blood/water	P_{bw} (dimensionless)	11.1 [g]
	Liver/blood	P_{lb} (dimensionless)	0.66 [a]
	Kidney/blood	P_{kb} (dimensionless)	0.66 [a]
Maximum reaction rate	Liver	V_{maxl} (mg/d)	0 (non-degradable)
Michaelis constant	Liver	K_{ml} (mg/L)	0 (non-degradable)
Effective skin permeability coefficient		K_p (cm/d)	0.0456 [e]

[f] $P_{ba} = P_{skw} \times P_{aw} / P_{skb}$

[g] $P_{bw} = P_{skw} / P_{skb}$

[a] Fisher et al. (1998)

[b] Abraham and Martins (2004)

[e] Xu et al. (2002).

Table SA3-1

Physiological parameter values for DCAA

		Parameter (unit)		Value
Body weight		b_w	(kg)	70 [a]
Tissue volume (assume unit density)[a]	Rapidly perfused	V_r	(L)	6.902 [a]
	Slowly perfused	V_s	(L)	49.64 [a]
	Plasma	V_p	(L)	3.08 [a]
	Skin	V_{sk}	(L)	2.45 [b]
	Liver	V_l	(L)	1.82 [a]
	Kidney	V_k	(L)	0.308 [a]
Alveolar ventilation rate		Q_{alv}	(L/d)	13940 [a]
Breathing rate		Q	(L/d)	19110 [c]
Ratio of alveolar ventilation rate to breathing rate		ϕ	(dimensionless)	0.729 [d]
Cardiac output		Q_t	(L/d)	9583 [a]
Blood flow	Rapidly perfused	Q_r	(L/d)	3067 [a]
	Slowly perfused	Q_s	(L/d)	1744 [a]
	Skin	Q_{sk}	(L/d)	556 [a]
	Liver	Q_l	(L/d)	2540 [a]
	Kidney	Q_k	(L/d)	1677 [a]
Body surface area exposed		A_{sk}	(cm^2)	20020 [a]
Urinary excretion		K_{utc}	(/d)	0.552

[a] Li et al. (2008)

[b] Poet et al. (2000)

[c] USEPA (2011)

[d] $\phi = Q_{alv}/Q$

Table SA3-2

Chemical-specific parameter values for DCAA

		Parameter(unit)	Value
Partition coefficients	Blood/air	P_{ba} (dimensionless)	8.78×10^{7} [f]
	Rapidly perfused/blood	P_{rb} (dimensionless)	1.08 [c]
	Slowly perfused/blood	P_{sb} (dimensionless)	0.11[c]
	Skin/blood	P_{skb} (dimensionless)	0.11[c]
	Skin/water	P_{skw} (dimensionless)	3.30 [b]
	Blood/water	P_{bw} (dimensionless)	30.0 [h]
	Liver/blood	P_{lb} (dimensionless)	1.08 [c]
	Kidney/blood	P_{kb} (dimensionless)	0.74 [c]
Maximum reaction rate	Liver	V_{maxl} (mg/d)	1.00×10^{6} [d]
Michaelis constant	Liver	K_{ml} (mg/L)	1000 [d]
Effective skin permeability coefficient		K_p (cm/d)	0.0456 [e]

[c] Li et al. (2008)

[b] Abraham and Martins (2004)

[d] Clewell et al. (2001)

[e] Xu et al. (2002)

[f] $P_{ba} = P_{skw} \times P_{aw} / P_{skb}$

[g] $P_{bw} = P_{skw} / P_{skb}$

Table SA4-1
Physiological parameter values for TCE and its metabolites in the TCE PBPK model.

			Parameter (unit)		Value
Body weight			b_w	(kg)	60 [a]
Tissue volume (assume unit density)[a]	TCE	Rapidly perfused	$V_{r\text{-}TCE}$	(L)	3.198 [a]
		Slowly perfused	$V_{s\text{-}TCE}$	(L)	24.12 [a]
		Fat	$V_{f\text{-}TCE}$	(L)	12.84 [a]
		Skin	$V_{sk\text{-}TCE}$	(L)	2.1 [e]
		Liver	$V_{l\text{-}TCE}$	(L)	1.56 [a]
		Kidney	$V_{k\text{-}TCE}$	(L)	0.24 [a]
		Gut	$V_{g\text{-}TCE}$	(L)	1.02 [a]
		Tracheobronchial	$V_{tb\text{-}TCE}$	(L)	0.042 [a]
		Placenta	$V_{pla\text{-}TCE}$	(L)	0.475 [a]
		Fetus	$V_{fet\text{-}TCE}$	(L)	2.326 [a]
	TCOH	Body	$V_{b\text{-}TCOH}$	(L)	46.121 [a]
		Liver	$V_{l\text{-}TCOH}$	(L)	1.56 [a]
		Kidney	$V_{k\text{-}TCOH}$	(L)	0.24 [a]
	TCAA	Body	$V_{b\text{-}TCA}$	(L)	46.121 [a]
		Liver	$V_{l\text{-}TCA}$	(L)	1.56 [a]
		Kidney	$V_{k\text{-}TCA}$	(L)	0.24 [a]
	DCAA	Rapidly perfused	$V_{r\text{-}DCA}$	(L)	7.061 [a]
		Slowly perfused	$V_{s\text{-}DCA}$	(L)	39.06 [a]
		Kidney	$V_{k\text{-}DCA}$	(L)	0.24 [a]
		Liver	$V_{l\text{-}DCA}$	(L)	1.56 [a]
		Plasma	$V_{p\text{-}DCA}$	(L)	2.64 [b]
Alveolar ventilation rate			Q_{alv}	(L/d)	11193 [a]
Ratio of alveolar ventilation rate to breathing rate			ϕ	(dimensionless)	0.729 [c]
Cardiac output			Q_t	(L/d)	8537 [a]
Blood flow	TCE	Rapidly perfused	$Q_{r\text{-}TCE}$	(L/d)	4100 [a]
		Slowly perfused	$Q_{s\text{-}TCE}$	(L/d)	1458 [a]
		Fat	$Q_{f\text{-}TCE}$	(L/d)	477 [a]
		Skin	$Q_{sk\text{-}TCE}$	(L/d)	826 [e]
		Liver	$Q_{l\text{-}TCE}$	(L/d)	421 [a]
		Gut	$Q_{g\text{-}TCE}$	(L/d)	1639 [a]
		Tracheobronchial	$Q_{tb\text{-}TCE}$	(L/d)	229 [a]
		Placenta	$Q_{pla\text{-}TCE}$	(L/d)	2043 [d]
	TCOH	Liver	$Q_{l\text{-}TCOH}$	(L/d)	2059 [a]
		Body	$Q_{b\text{-}TCOH}$	(L/d)	7530 [a]
		Kidney	$Q_{k\text{-}TCOH}$	(L/d)	1604 [a]
	TCAA	Liver	$Q_{l\text{-}TCA}$	(L/d)	2059 [a]
		Body	$Q_{b\text{-}TCA}$	(L/d)	7530 [a]
		Kidney	$Q_{k\text{-}TCA}$	(L/d)	1604 [a]
	DCAA	Rapidly perfused	$Q_{r\text{-}DCA}$	(L/d)	6372 [a]
		Slowly perfused	$Q_{s\text{-}DCA}$	(L/d)	2761 [a]
		Liver	$Q_{l\text{-}DCA}$	(L/d)	2060 [a]
		Kidney	$Q_{k\text{-}DCA}$	(L/d)	1604 [a]
Body surface area exposed			A_{sk}	(cm^2)	17160 [a]

[a] Clewell et al. (2000)
[b] Li et al. (2008)
[c] USEPA (2011)
[d] Abduljalil et al. (2012)
[e] Poet et al. (2000)

Table SA4-2
Chemical-specific parameter values for TCE and its metabolites in the TCE PBPK model.

			Parameter (unit)		value
Partition coefficients	TCE	Blood/air	P_{ba}	(dimensionless)	9.2 [a]
	TCE	Rapidly perfused/blood	$P_{rb\text{-}TCE}$	(dimensionless)	6.8 [a]
		Slowly perfused/blood	$P_{sb\text{-}TCE}$	(dimensionless)	2.3 [a]
		Fat/blood	$P_{fb\text{-}TCE}$	(dimensionless)	73 [a]
		Skin/blood	$P_{skb\text{-}TCE}$	(dimensionless)	1.45 [b]
		Skin/water	$P_{skw\text{-}TCE}$	(dimensionless)	53 [b]
		Liver/blood	$P_{lb\text{-}TCE}$	(dimensionless)	6.8 [a]
		Placenta/blood	$P_{pb\text{-}TCE}$	(dimensionless)	6.8 [a]
	TCOH	Body/blood	$P_{bb\text{-}TCOH}$	(dimensionless)	0.91 [c]
		Kidney/blood	$P_{kb\text{-}TCOH}$	(dimensionless)	2.15 [c]
		Liver/blood	$P_{lb\text{-}TCOH}$	(dimensionless)	0.59 [c]
	TCAA	Body/blood	$P_{bb\text{-}TCA}$	(dimensionless)	0.52 [c]
		Kidney/blood	$P_{kb\text{-}TCA}$	(dimensionless)	0.66 [c]
		Liver/blood	$P_{lb\text{-}TCA}$	(dimensionless)	0.66 [c]
	DCAA	Rapidly perfused/blood	$P_{rb\text{-}DCA}$	(dimensionless)	1.08 [d]
		Slowly perfused/blood	$P_{sb\text{-}DCA}$	(dimensionless)	0.11 [d]
		Kidney/blood	$P_{kb\text{-}DCA}$	(dimensionless)	0.74 [d]
		Liver/blood	$P_{lb\text{-}DCA}$	(dimensionless)	1.08 [d]
Maximum reaction rate	TCE	Liver	V_{ml}	(mg/d)	215.6 [a]
		Tracheobronchial	V_{mt}	(mg/d)	2.33 [a]
	TCOH	Liver(TCOH→TCA)	V_{mo}	(mg/d)	12935 [a]
		Liver(TCOH→TCOG)	V_{mg}	(mg/d)	2587 [a]
		Liver(TCOH→DCA)	V_{mr}	(mg/d)	51.7 [a]
	DCAA	Liver	V_{md}	(mg/d)	985098 [a]
Michaelis constant	TCE	Liver	K_{ml}	(mg/L)	1.5 [a]
		Tracheobronchial	K_{mt}	(mg/L)	1.5 [a]
	TCOH	Liver(TCOH→TCA)	K_{mo}	(mg/L)	250 [a]
		Liver(TCOH→TCOG)	K_{mg}	(mg/L)	25 [a]
		Liver(TCOH→DCA)	K_{mr}	(mg/L)	10 [a]
	DCAA	Liver	K_{md}	(mg/L)	1000 [a]
Production	TCE	Liver(TCE→DCVC)	K_f	(/d)	0.129 [a]
Fraction of metabolized TCE	TCE	Liver(TCE→TCOH)	P_{TCOH}	(dimensionless)	0.92 [a]
		Liver(TCE→TCA)	P_{TCA}	(dimensionless)	0.08 [a]
Plasma protein bind	DCAA	Maximum capacity	B_{max}	(mg)	0.06 [a]
		Affinity constant	K_{mb}	(mg/L)	0.001 [a]
		Dissociation constant	K_{unb}	(/d)	3.84 [a]
Urinary excretion	TCAA	Kidney	K_{utc}	(/d)	0.198 [a]
	DCAA	Kidney	CL_r	(/d)	0.198 [a]
Effective skin permeability coefficient	TCE		K_p	(cm/d)	0.408 [a,b]
Molecular weight	TCE		MW_{TCE}	(g/mol)	131.38
	TCOH		MW_{TCOH}	(g/mol)	149.4
	TCAA		MW_{TCA}	(g/mol)	163.4 [e]
	DCAA		MW_{DCA}	(g/mol)	128.9 [e]

[a] (Clewell et al. 2000), Clewell et al. (2001)
[b] Poet et al. (2000)
[c] Fisher et al. (1998)
[d] Li et al. (2008)
[e] Jin et al. (2012)

Table SA5-1

Physiological parameter values for PCE and its metabolite (TCAA) in the PCE PBPK model.

			Parameter (unit)		Value
Body weight			b_w	(kg)	70 [a]
Tissue volume (assume unit density)[a]	PCE	Rapidly perfused	$V_{r\text{-}PCE}$	(L)	5.572 [a]
		Slowly perfused	$V_{s\text{-}PCE}$	(L)	28.35 [a]
		Fat	$V_{f\text{-}PCE}$	(L)	14.7 [a]
		Skin	$V_{sk\text{-}PCE}$	(L)	2.45 [b]
		Liver	$V_{l\text{-}PCE}$	(L)	1.82 [a]
		Kidney	$V_{k\text{-}PCE}$	(L)	0.308 [a]
	TCAA	Body	$V_{b\text{-}PCE}$	(L)	51.072 [a]
		Liver	$V_{l\text{-}PCE}$	(L)	1.82 [a]
		Kidney	$V_{k\text{-}PCE}$	(L)	0.308 [a]
Alveolar ventilation rate			Q_{alv}	(L/d)	13939 [a]
Ratio of alveolar ventilation rate to breathing rate			ϕ	(dimensionless)	0.968 [c]
Cardiac output			Q_t	(L/d)	9583 [a]
Blood flow	PCE	Rapidly perfused	$Q_{r\text{-}PCE}$	(L/d)	2779 [a]
		Slowly perfused	$Q_{s\text{-}PCE}$	(L/d)	1840 [a]
		Fat	$Q_{f\text{-}PCE}$	(L/d)	479 [a]
		Skin	$Q_{sk\text{-}PCE}$	(L/d)	556 [b]
		Liver	$Q_{l\text{-}PCE}$	(L/d)	2204 [a]
		Kidney	$Q_{k\text{-}PCE}$	(L/d)	1725 [a]
	TCAA	Body	$Q_{b\text{-}TCA}$	(L/d)	5654 [a]
		Liver	$Q_{l\text{-}TCA}$	(L/d)	2204 [a]
		Kidney	$Q_{k\text{-}TCA}$	(L/d)	1725 [a]
Body surface area exposed			A_{sk}	(cm^2)	20020 [a]

[a] Covington et al. (2007)

[b] Poet et al. (2002)

[c] USEPA (2011)

Table SA5-2

Chemical-specific parameter values for PCE and its metabolite (TCAA) in the PCE PBPK model.

			Parameter (unit)		Value
Partition coefficients	PCE	Blood/air	P_{ba}	(dimensionless)	11.58 [a]
		Rapidly perfused/blood	$P_{rb\text{-}PCE}$	(dimensionless)	5.06 [a]
		Slowly perfused/blood	$P_{sb\text{-}PCE}$	(dimensionless)	6.11 [a]
		Fat/blood	$P_{fb\text{-}PCE}$	(dimensionless)	125.2 [a]
		Skin/blood	$P_{skb\text{-}PCE}$	(dimensionless)	3.58 [b]
		Skin/water	$P_{skw\text{-}PCE}$	(dimensionless)	32.1 [b]
		Liver/blood	$P_{lb\text{-}PCE}$	(dimensionless)	5.28 [a]
		Kidney/blood	$P_{kb\text{-}PCE}$	(dimensionless)	5.06 [a]
		Placenta/blood	$P_{pb\text{-}PCE}$	(dimensionless)	5.06 [a]
	TCAA	Body/blood	$P_{bb\text{-}TCA}$	(dimensionless)	0.52 [c]
		Liver/blood	$P_{lb\text{-}TCA}$	(dimensionless)	0.52 [c]
		Kidney/blood	$P_{kb\text{-}TCA}$	(dimensionless)	0.52 [c]
Maximum reaction rate		Liver	V_{maxl}	(mg/d)	162.6 [a]
		Kidney	V_{maxk}	(mg/d)	162.6 [a]
Michaelis constant		Liver	K_{ml}	(mg/L)	7.7 [a]
		Kidney	K_{mk}	(mg/L)	7.7 [a]
Fraction of liver PCE metabolism		Liver	*FTCAliv*	(dimensionless)	0.585 [a]
		Kidney	*FTCAkid*	(dimensionless)	0.765 [a]
Fraction of TCA in kidney excreted in urine			*Frac*	(dimensionless)	0.763 [a]
Fraction of liver MFO activity in kidney			*Frack*	(dimensionless)	0.251 [a]
TCA elimination			*kUC*	(d^{-1})	0.008 [a]
Effective skin permeability coefficient of PCE			K_p	(cm/d)	0.786 [d]

[a] Clewell et al. (2001)

[b] Poet et al. (2000)

[c] Fisher et al. (1998)

[d] USEPA (2004)

Abbreviations

Symbols	Definition
a_i	Coefficient for the effect of cooking water on food (dimensionless)
A_D	Daily oral intake (mg/day)
A_f	Allocation factor (%)
A_{sk}	Body surface area (cm^2)
$b_k(r)$ [1)]	Coefficient for the effect of water evaporation on the air (dimensionless, k = bathroom, kitchen, or residence)
b_w	Body weight (kg)
b_h	Body height (cm)
C_a	Concentration in inhaled air (mg/L)
$\overline{C_a}(r)$	Daily-average concentration in inhaled air (mg/L)
$C_{air,w,k}(r)$ [1)]	Concentration in inhaled air in an area (k = bathroom, kitchen, or residence) under the influence from tap water (mg/L)
$C_{air,outdoor}(r)$ [1)]	Concentration in outdoor air (mg/L)
C_{alv}	Concentration in alveolar air (mg/L)
C_{art}	Concentration in arterial blood (mg/L)
C_d	Concentration in water for dermal adsorption (mg/L)
$\overline{C_d}(r)$ [1)]	Daily-average concentration in water for dermal adsorption (mg/L)
$C_{food,w,i}$	Concentration in i^{th} food group after cooking with tap water (mg/g)
$C_{food,0,i}$	Concentration in i^{th} food group after cooking with pure water (mg/g)
C_{ven}	Concentration in mixed venous blood (mg/L)
C_{vf}	Concentration in venous blood leaving fat (mg/L)
C_{vk}	Concentration in venous blood leaving the kidneys (mg/L)
C_{vl}	Concentration in venous blood leaving the liver (mg/L)
C_{vr}	Concentration in venous blood leaving rapidly perfused tissues (mg/L)
C_{vs}	Concentration in venous blood leaving slowly perfused tissues (mg/L)
C_{vsk}	Concentration in venous blood leaving skin (mg/L)
C_w	Concentration in tap water (mg/L)
D_D	Dermal potential dose [mg/(kg-body d)]
D_{DO}	Oral-equivalent dermal potential dose [mg/(kg-body d)]
D_I	Inhalation potential dose [mg/(kg-body d)]
D_{IO}	Oral-equivalent inhalation potential dose [mg/(kg-body d)]
D_O	Oral potential dose [mg/(kg-body d)]
D_T	Total oral-equivalent potential dose [mg/(kg-body d)]
E_D	Dermal biologically effective dose [mg/(kg-organ d)]
E_I	Inhalation biologically effective dose [mg/(kg-organ d)]
E_O	Oral biologically effective dose [mg/(kg-organ d)]
G_v	Guideline value (mg/L)
K_{mk}	Michaelis constant for enzymatic reaction for the kidneys (mg/L)
K_{ml}	Michaelis constant for enzymatic reaction for the liver (mg/L)
K_p	Effective skin permeability coefficient (cm/d)
$I_{food,i,j}(r)$ [1)]	Daily intake of j^{th} food in i^{th} food group (g/d)
I_{water}	Daily drinking water consumption (L/d)
P_{ba}	Blood/air partition coefficient (dimensionless)
P_{fb}	Fat/blood partition coefficient (dimensionless)
P_{kb}	Kidney/blood partition coefficient (dimensionless)
P_{lb}	Liver/blood partition coefficient (dimensionless)
P_{rb}	Rapidly perfused /blood partition coefficient (dimensionless)
P_{sb}	Slowly perfused /blood partition coefficient (dimensionless)
P_{skb}	Skin/blood partition coefficient (dimensionless)
P_{skw}	Skin/water partition coefficient (dimensionless)
Q	Breathing rate (L/d)
Q_{alv}	Alveolar ventilation rate (L/d)
Q_f	Blood flow rate to fat (L/d)
Q_k	Blood flow rate to the kidneys (L/d)
Q_l	Blood flow rate to the liver (L/d)
Q_r	Blood flow rate to rapidly perfused tissues (L/d)

Q_s	Blood flow rate to slowly perfused tissues (L/d)
Q_{sk}	Blood flow rate to skin (L/d)
Q_t	Cardiac output (L/d)
t	Time (d)
$t_{bathroom}(r)$ [1)]	Time spent in bathroom per day (dimensionless)
$t_{kitchen}(r)$ [1)]	Time spent in kitchen per day (dimensionless)
$t_{residence}(r)$ [1)]	Time spent in residence per day (dimensionless)
$t_{outdoor}(r)$ [1)]	Time spent outdoors per day (dimensionless)
V_f	Volume of fat (L)
V_l	Volume of the liver (L)
V_k	Volume of the kidneys (L)
V_{maxl}	Maximum enzymatic reaction rate for the liver (mg/d)
V_{maxk}	Maximum enzymatic reaction rate for the kidneys (mg/d)
V_r	Volume of rapidly perfused tissues (L)
V_s	Volume of slowly perfused tissues (L)
V_{sk}	Volume of skin (L)
α	Ratio of effective doses by single/continuous exposure (dimensionless)
α_1	Ratio of oral effective doses by single/continuous exposure (dimensionless)
α_2	Ratio of inhalation effective doses by single/continuous exposure (dimensionless)
α_3	Ratio of dermal effective doses by single/continuous exposure (dimensionless)
$\alpha_{2/1}$	Ratio of α_2 to α_1 (dimensionless)
$\alpha_{3/1}$	Ratio of α_3 to α_1 (dimensionless)
β	Ratio of effective/potential dose at a constant continuous administration (kg-body d/kg-organ)
β_1	Ratio of oral effective/potential dose at a constant continuous administration (kg-body d/kg-organ)
β_2	Ratio of inhalation effective/potential dose at a constant continuous administration (kg-body d/kg-organ)
β_3	Ratio of dermal effective/potential dose at a constant continuous administration (kg-body d/kg-organ)
$\beta_{2/1}$	Ratio of β_2 to β_1 (dimensionless)
$\beta_{3/1}$	Ratio of β_3 to β_1 (dimensionless)
ϕ	Ratio of alveolar ventilation rate to breathing rate (dimensionless)

1) "(r)" indicates Monte-Carlo input.

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Supplementary Information B

Monte-Carlo and multi-exposure assessment for the derivation of criteria for disinfection byproducts and volatile organic compounds in drinking water: allocation factors and liter-equivalents per day

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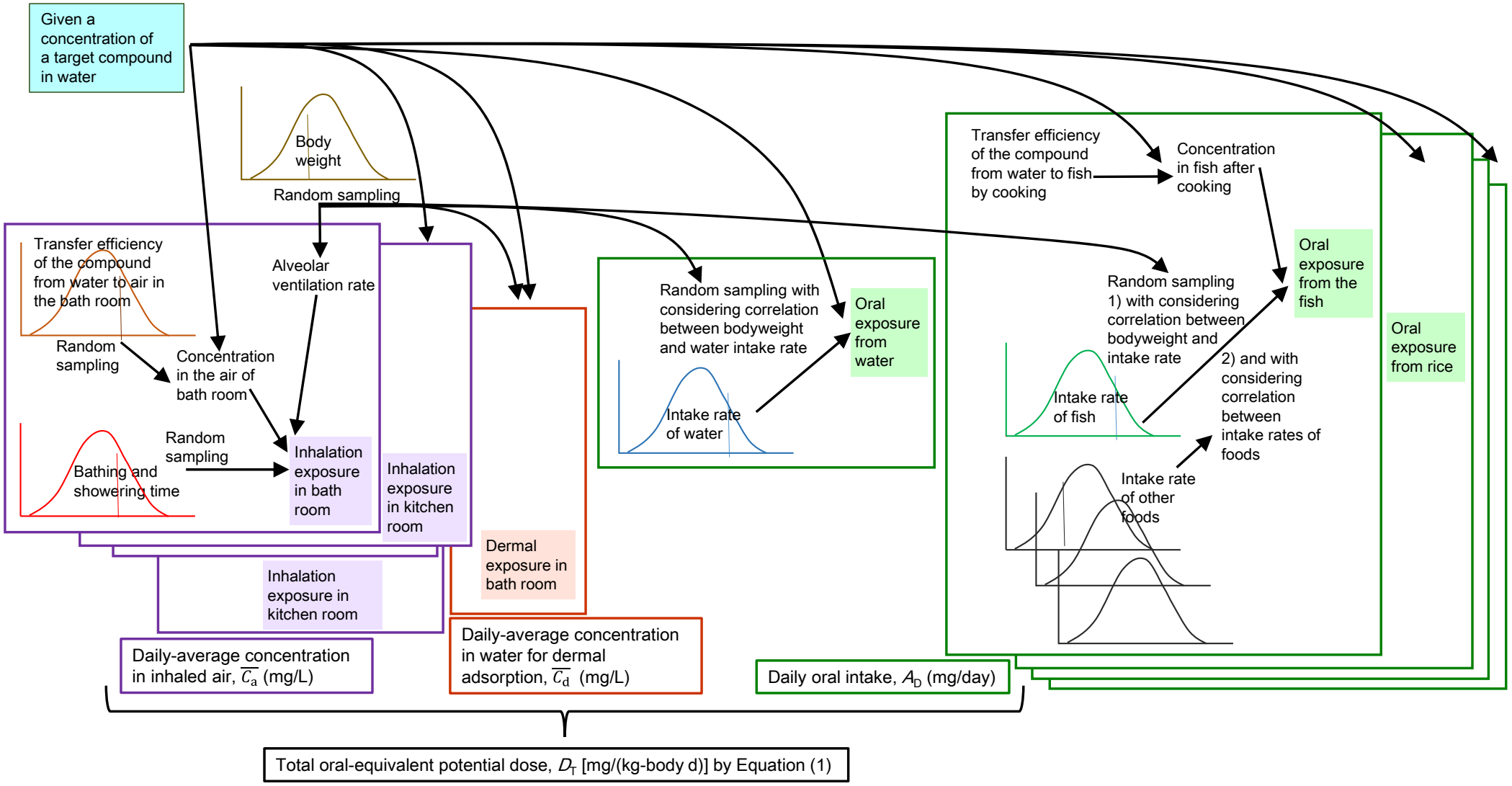

Fig. SB1. Flow chart of the Monte-Carlo method to calculate the probability distribution of total oral-equivalent exposure.

1. Exposure estimation procedure (Niizuma et al. 2013)

Foods were categorized into 17 groups. The indirect ingestion of chemicals in tap water through cooking was taken into account by using Equation (SB1).

$$C_{\mathrm{food,w},i} = a_i \times C_{\mathrm{w}} + C_{\mathrm{food},0,i} \quad \text{(SB1)}$$

The concentration in each food group was multiplied by the daily intake of that food group, and the daily oral exposure was calculated with Equation (SB2).

$$A_{\mathrm{D}} = C_{\mathrm{w}} I_{\mathrm{water}} + \sum_{i=1}^{17} \left[C_{\mathrm{food,w},i} \sum_j I_{\mathrm{food},i,j}(\mathrm{r}) \right] \quad \text{(SB2)}$$

Daily intake of each food group was determined randomly by the Monte Carlo method based on the probability distributions of the data in the National Health and Nutrition Survey database (MHLWJ 2006).

Ambient air associated with exposure from inhalation was classified into one of five categories based on location: (1) bathroom for bathing and showering; (2) kitchen; (3) living room; (4) other indoor areas including bedroom in a residence; and (5) other areas including outdoors and work places (hereafter simply referred to as outdoors). The concentration of a volatile compound in the first three areas was affected by volatilization from tap water and was expressed by Equation (SB3)

$$C_{\mathrm{air,w},k}(\mathrm{r}) = b_k(\mathrm{r}) \times C_{\mathrm{w}} + C_{\mathrm{air,outdoor}}(\mathrm{r}) \quad \text{(SB3)}$$

Daily average inhalation concentrations were estimated with Equation (SB4)

$$\begin{aligned} \overline{C_{\mathrm{a}}}(\mathrm{r}) = {} & C_{\mathrm{air,w,bathroom}}(\mathrm{r}) t_{\mathrm{bathroom}}(\mathrm{r}) + C_{\mathrm{air,w,kitchen}}(\mathrm{r}) t_{\mathrm{kitchen}}(\mathrm{r}) \\ & + C_{\mathrm{air,w,living\ room}}(\mathrm{r}) t_{\mathrm{living\ room}}(\mathrm{r}) + C_{\mathrm{air,w,regidence}}(\mathrm{r}) t_{\mathrm{regidence}}(\mathrm{r}) \\ & + C_{\mathrm{air,outdoor}}(\mathrm{r}) t_{\mathrm{outdoor}}(\mathrm{r}) \end{aligned} \quad \text{(SB4)}$$

Daily average dermal exposure concentrations were estimated with Equation (SB5)

$$\overline{C_{\mathrm{d}}}(\mathrm{r}) = C_{\mathrm{w}} t_{\mathrm{bathroom}}(\mathrm{r}) \quad \text{(SB5)}$$

2. Parameter values for the target compounds

2.1 TCM

The data of Niizuma et al. (2013) were used for the values of a_i and $b_k(\mathrm{r})$.

2.2 BDCM and DBCM

We used the data from Itoh and Asami (2010), the same data source used by Niizuma et al. (2013). The values of a_i and $b_k(\mathrm{r})$ were evaluated by using Equations (SB1) and (SB3), respectively.

2.3 TBM

The values of a_i could not be determined from Itoh and Asami (2010) because the TBM concentrations in their data were all below the limit of detection. For some foods, we used the a_i value of DBCM as a substitute for the a_i of TBM when the a_i values decreased in the order TCM, BDCM, and DBCM. In other words, we assumed that the a_i value of TBM was close to that of DBCM. When no such decreasing trend was apparent for other foods, the average a_i value of TCM, BDCM, and DBCM was used for TBM. It is important to note that the contribution of foods to total TBM exposure was found to be small (< 5%). Any error associated with this assumption should therefore have had little effect on the estimation of total TBM exposure. To determine the values of $b_k(\mathrm{r})$, we used the data from Itoh and Asami (2010), the same source of data used by Niizuma et al. (2013)

2.4 DCAA and TCAA

The values of a_i were determined with Equation (SB1) using data from Itoh and Asami (2010). The value of $b_k(\mathrm{r})$ was assumed to be zero because of the very low volatility of DCAA and TCAA.

2.5 TCE and PCE

The a_i values for the 1st food group (cereals), the 2nd food group (potatoes), 4th food group (beans), the 6th food group (vegetables), and 16th food group (nonessential grocery items) were estimated from a regression equation between a_i and log Kow, a relationship that had previously been established for TCM, BDCM, DBCM, DCAA, and TCAA. Correlations were not observed for the other food groups. For those food groups, the highest a_i value in each food group was used, the result being that the estimated exposures were on the high-risk side. Nonetheless, the contribution of food to exposure was negligibly small (< 0.2%). Therefore, any error associated with this estimation should be very small in the total exposure estimation.

No data have been reported for the effect of tap water on the TCE and PCE concentrations in bathrooms and residences. Therefore, the values of $b_k(\mathrm{r})$ were estimated with the following procedure.

2.5.1 Measurements of TCE, PCE, and THMs concentrations in a bathroom.

Waters containing TCE, PCE, and THMs were prepared by adding reagent-grade TCE, PCE, TCM, DBCM, BDCM, and TBM to warm tap water (0.2 m^3, 40 °C) in a tank to produce concentrations of 10 μg/L each. The water was then allowed to flow through a shower head at a rate of 7.4 L /min in a bathroom (2.0 × 1.6 × 2.2 m^3) under several different conditions: with or without a bathtub filled with the water and with or without ventilation. After passing through a dehumidifier tube (in-line trap for gas sampling, Sibata Scientific Technology Ltd., Saitama, Japan), 5 L of the air in the bathroom was drawn by a pump through three sampling tubes placed in series (Carbon Beads Active: Standard Type, Sibata Scientific Technology Ltd.) at a rate of 0.5 L/min. The TCE, PCE, and THM concentrations in the water were quantitatively determined by purge-and-trap gas chromatography/mass spectrometry (P&T-GC/MS, P&T: GL Sciences GC/MS, Shimadzu Co. Kyoto, Japan). The quantities of TCE, PCE, and THMs in a tube were analyzed by GC-MS (Agilent Technologies Japan, Ltd., Tokyo, Japan) after they were desorbed from the tube into carbon disulfide. Figure SB2 shows the concentrations of TCE, PCE, and THMs in the bathroom air.

2.5.2 Determination of the b_k values for TCE and PCE.

Coefficients for the effect of evaporation from water to air (b_k) were calculated from the concentrations in water and air using Equation (SB3). These b_k values varied as a function of

bath conditions. Among the compounds, the TCE b_k values were the highest, followed by the b_k values for PCE and TCM. The b_k values of TCE were 3.75 times those of TCM (left panel of Fig. SB2), which had the highest b_k value of the THMs and the closest to the b_k values of TCE. The b_k values of TCE were 4.46 times those of BDCM (right panel of Fig. SB2). As shown in Fig. SB3, the product of the $b_k(\mathrm{r})$ (Monte-Carlo inputs) of TCM (Niizuma et al. 2013) and 3.75 was the same as the product of the $b_k(\mathrm{r})$ of BDCM and 4.46. The equality of these products was probably due to the high concentrations of TCM and BDCM, which made it possible to obtain an accurate estimation of $b_k(\mathrm{r})$. We used the data in Fig. SB3 as the $b_k(\mathrm{r})$ values of TCE. The same procedure used for the TCE calculations was applied to PCE, and the results produced qualitatively similar trends to the $b_k(\mathrm{r})$ values of TCM and BDCM (Figs. SB4 and SB5). We used the data in Fig. SB5 as the $b_k(\mathrm{r})$ values of PCE.

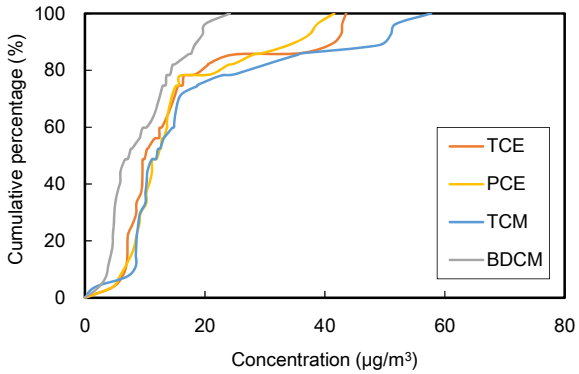

Fig. SB2. Concentrations of TCE, PCE, TCM, and BDCM in bathrooms (data variability reflects different conditions (bathtub filled or not filled with water and bathroom with or without ventilation).

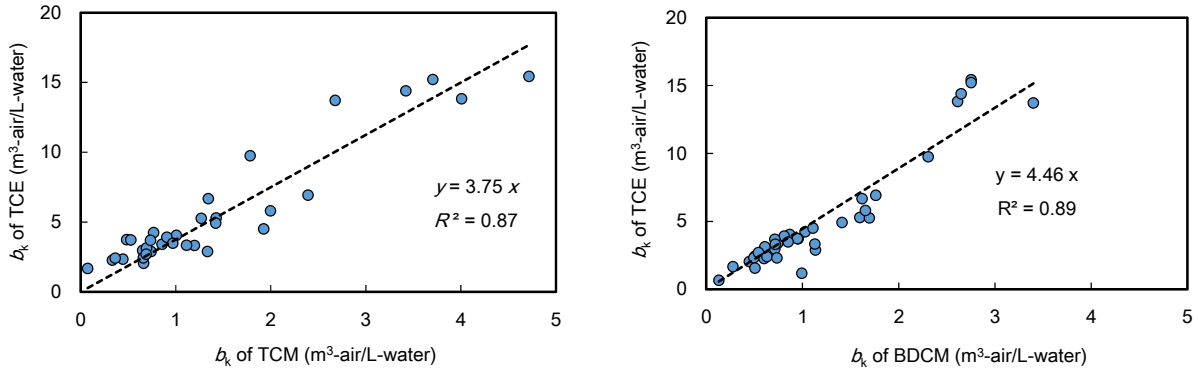

Fig. SB3. Plots of TCE b_k values against TCM b_k values (left panel) and against BDCM b_k values (right panel).

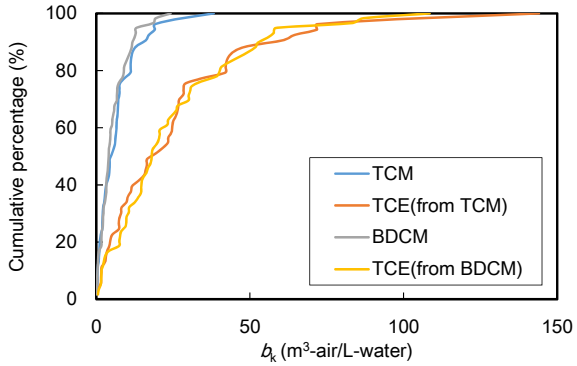

Fig. SB4. The distributions of the $b_k(\mathrm{r})$ values of TCM multiplied by 3.75 and the $b_k(\mathrm{r})$ values of BDCM multiplied by 4.46.

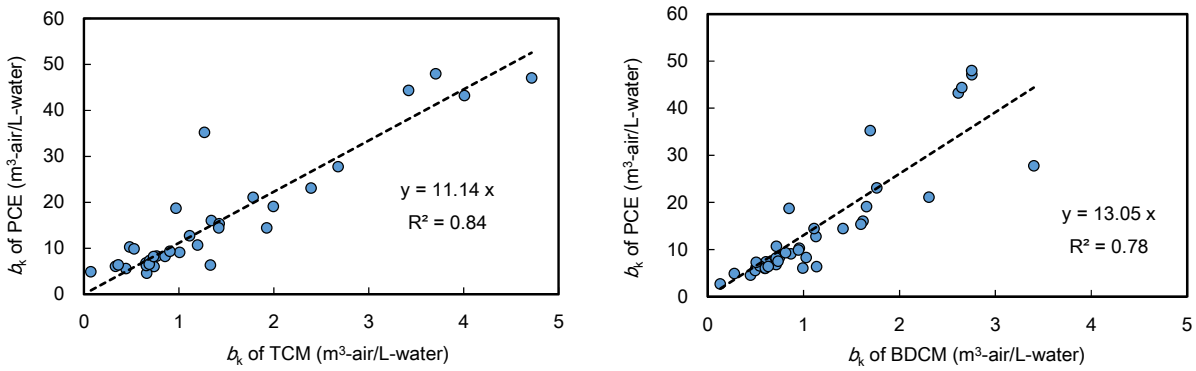

Fig. SB5. Plots of PCE b_k values against TCM b_k values (left panel) and against BDCM b_k values (right panel).

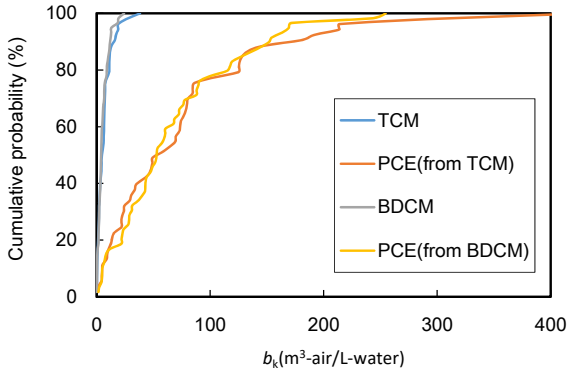

Fig. SB6. The distribution of the $b_k(\mathrm{r})$ values of TCM multiplied by 11.14 and the $b_k(\mathrm{r})$ values of BDCM multiplied by 13.05.

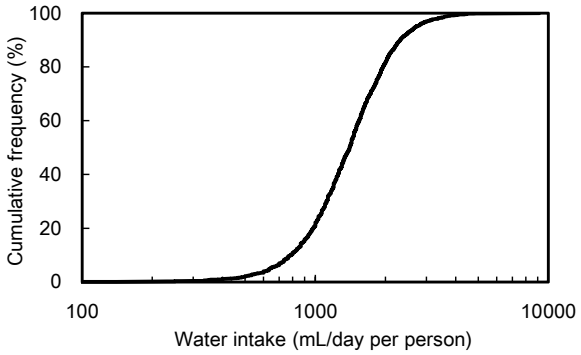

Fig. SB7. Distribution of daily water intake per person (Matsui 2013)

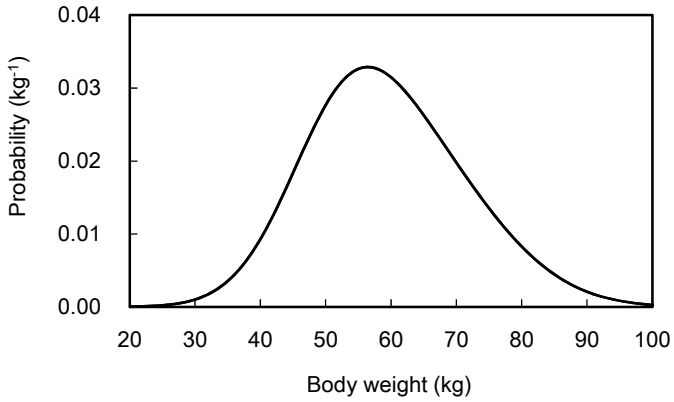

Fig. SB8. Distribution body weights of Japanese adults (Statistics Bureau 2014)

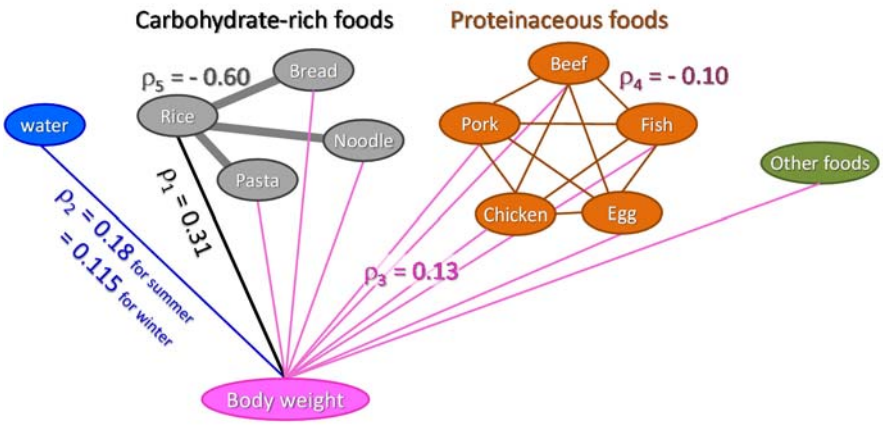

Fig. SB9. Structure of correlations between food intake, water intake, and body weight.

The values of the correlation coefficient ρ_1 (water intake versus body weight) and ρ_2 (rice intake versus body weight) were determined using the results of a survey for drinking water consumption (Matsui 2013). The value of the correlation coefficient ρ_4 was determined based on a comparison of the standard deviation of the protein intake distribution obtained from the Mote Carlo simulation output versus that of the Japanese population (MHLWJ 2013). The value of the correlation coefficient ρ_5 was determined based on a comparison of the standard deviation of carbohydrate intake distribution obtained from the Monte Carlo simulation output versus that of the Japanese population. The value of the correlation coefficient ρ_3 was determined based on a comparison of the standard deviations of total food intake mass and total energy intake from the Monte Carlo simulation output versus those of the Japanese population.

Table SB1

Examples of $R_{1/2}$ and $R_{1/3}$ calculations

Exposed substance	Target substance	Endpoint (AUC calculation)	Oral exposure $\frac{A_{\text{oral}}}{AUC_{\text{oral}}/t_{\text{oral}}}$	Inhalation exposure $\frac{C_{\text{inhalation}}Q_{alv}}{AUC_{\text{inhalation}}/t_{\text{inhalation}}}$	Dermal exposure $\frac{AUC_{\text{dermal}}/t_{\text{dermal}}}{C_{\text{dermal}}K_{\text{p}}A_{\text{sk}}\times 10^{-3}\,L/\text{cm}^3}$	b_{w}	Q_{alv}	K_{p}	A_{sk}	$R_{2/1}$	$R_{3/1}$
			Dimensionless	Dimensionless	Dimensionless	(kg)	(m^3/d)	(cm/d)	(cm^3)	(dimensionless)	(dimensionless)
TCM	TCM	Liver (metabolic rate)	1.066	1.943	1.967	70	13.9	1.2	20020	0.549	0.542
BDCM	BDCM	Liver (metabolic rate)	1.034	1.290	1.308	70	13.9	0.54	20020	0.802	0.791
DBCM	DBCM	Liver (metabolic rate)	1.031	1.160	1.167	70	13.9	1.25	20020	0.888	0.883
TBM	TBM	Liver (metabolic rate)	1.013	1.080	1.078	70	13.9	0.26	20020	0.939	0.940

Exposed substance	Target substance	Endpoint (dose metric)	Oral exposure $\frac{A_{\text{oral}}}{AUC_{\text{oral}}/t_{\text{oral}}}$	Inhalation exposure $\frac{C_{\text{inhalation}}Q_{alv}}{AUC_{\text{inhalation}}/t_{\text{inhalation}}}$	Dermal exposure $\frac{AUC_{\text{dermal}}/t_{\text{dermal}}}{C_{\text{dermal}}K_{\text{p}}A_{\text{sk}}\times 10^{-3}\,L/\text{cm}^3}$	b_{w}	Q_{alv}	K_{p}	A_{sk}	$R_{2/1}$	$R_{3/1}$
			L/d	L/d	L/d	(kg)	(m^3/d)	(cm/d)	(cm^3)	(dimensionless)	(dimensionless)
DCAA	DCAA	Liver (plasma concentration)	1005	1005	1005	70	13.9	0.0456	20020	1.00	1.00
TCAA	TCAA	Liver (plasma concentration)	0.0542	0.0542	0.0542	70	13.9	0.0456	20020	1.00	1.00
TCE	TCE	Placenta (plasma concentration)	6178	2759	2302	60	11.2	0.408	17160	2.24	2.68
	DCAA (metabolite)	Placenta (plasma concentration)	36490	65070	57130	60	11.2	-	17160	0.561	0.639
	TCAA (metabolite)	Placenta (plasma concentration)	0.0681	0.1217	0.1018	60	11.2	-	17160	0.560	0.669
PCE	PCE	Liver (plasma concentration)	807	1223	1221	70	13.9	0.786	20020	0.660	0.661
	TCAA (metabolite)	Liver (plasma concentration)	4.03	5.99	5.95	70	13.9	-	20020	0.672	0.677

Table SB2

Values of $b_k(\mathrm{r})$ and transfer efficiency

	Parameter (unit)		TCM	DBCM	BDCM	TBM	DCAA	TCAA	TCE	PCE
Median $b_k(\mathrm{r})$ value at bathrooms	$b_k(\mathrm{r})$	m^3-air/L-water	5.11	5.70	4.03	2.81	0.09	0.05	18.2	53.8
Transfer efficiency [g]	ϕ	(dimensionless)	34.6	8.1	20.5	5.3	0.0000877	0.000133	71.2	96.8
Diffusion coefficient in air [c]	D_a	(m^2/s)	0.091	0.084	0.086	0.082	0.085	0.077	0.083	0.076
Diffusion coefficient in water [d]	D_l	10^{-5} (m^2/s)	1.05	1.02	1.04	1.01	1.00	0.89	0.96	0.87
Henry constant	H	(Pa•m^3/mol)	372[a]	82.1[b]	215[c]	54.2[d]	0.000849[e]	0.00137[e]	998[f]	1790[a]
Temperature	T	(°C)	24[a]	25	25[c]	25[d]	25 [e]	25 [e]	25[f]	24 [a]
Molar mass	M_A	(g/mol)	119.38	208.27	163.83	252.73	128.94	163.39	131.39	165.83
Molar volume [h]	V_B	(m^3/mol)	76.98	84.96	82.86	87.06	88.38	106.66	93.48	111
Molar volume by the Lebas method [h]	V_B'	(m^3/mol)	92.3	97.1	94.7	99.5	101	121.9	107.1	128

Transfer efficiency for radon [g]	ϕ_{RN}	(dimensionless)	0.66
Overall mass-transfer coefficient for radon [g]	K_{RN}	(m/s)	5.0×10^{-7}
Gas constant	R	(Pa/L/mol/K)	8314.51
Temperature	T	(K)	298
Molar mas of air [h]	M_A	(g/mol)	28.97
Molar volume of air [h]	V_A	(m^3/mol)	20.1
Pressure	P	(atm)	1.0
Viscosity of water [h]	η_w	(cP)	0.8904

[a] Gossett (1987)

[b] EPI Suite (2012)

[c] Warner et al. (1987)

[d] Munz and Roberts (1987)

[e] Bowden et al. (1998)

[f] Leighton and Calo (1981)

[g] McKone (1987), Yoshida and Nakanishi (2006)

[h] Lyman et al. (1990)

$$D_a = \frac{10^{-3}T^{1.75}\sqrt{M_r}}{P\left(V_A^{1/3}+V_B^{1/3}\right)^2}$$

$$M_r = \frac{M_A + M_B}{M_A M_B}$$

$$D_l = \frac{13.26\times10^{-5}}{\eta_w^{1.14}V_B'^{0.589}}$$

Abbreviations

Symbols	Definition
a_i	Coefficient for the effect of cooking water on food (dimensionless)
A_D	Daily oral intake (mg/day)
A_f	Allocation factor (%)
A_{sk}	Body surface area (cm^2)
$b_k(r)$ [1)]	Coefficient for the evaporation effect from water to air (dimensionless, k = bathroom, kitchen, or residence)
b_w	Body weight (kg)
b_h	Body height (cm)
C_a	Concentration in inhaled air (mg/L)
$\overline{C_a}(r)$	Daily-average concentration in inhaled air (mg/L)
$C_{air,w,k}(r)$ [1)]	Concentration in inhaled air in an area (k = bathroom, kitchen, or residence) under the influence from tap water (mg/L)
$C_{air,outdoor}(r)$ [1)]	Concentration in outdoor air (mg/L)
C_{alv}	Concentration in alveolar air (mg/L)
C_{art}	Concentration in arterial blood (mg/L)
C_d	Concentration in water for dermal adsorption (mg/L)
$\overline{C_d}(r)$ [1)]	Daily-average concentration in water for dermal adsorption (mg/L)
$C_{food,w,i}$	Concentration in i^{th} food group after cooking with tap water (mg/g)
$C_{food,0,i}$	Concentration in i^{th} food group after cooking with pure water (mg/g)
C_{ven}	Concentration in mixed venous blood (mg/L)
C_{vf}	Concentration in venous blood leaving fat (mg/L)
C_{vk}	Concentration in venous blood leaving the kidneys (mg/L)
C_{vl}	Concentration in venous blood leaving the liver (mg/L)
C_{vr}	Concentration in venous blood leaving rapidly perfused tissues (mg/L)
C_{vs}	Concentration in venous blood leaving slowly perfused tissues (mg/L)
C_{vsk}	Concentration in venous blood leaving skin (mg/L)
C_w	Concentration in tap water (mg/L)
D_D	Dermal potential dose [mg/(kg-body d)]
D_{DO}	Oral-equivalent dermal potential dose [mg/(kg-body d)]
D_I	Inhalation potential dose [mg/(kg-body d)]
D_{IO}	Oral-equivalent inhalation potential dose [mg/(kg-body d)]
D_O	Oral potential dose [mg/(kg-body d)]
D_T	Total oral-equivalent potential dose [mg/(kg-body d)]
E_D	Dermal biologically effective dose [mg/(kg-organ d)]
E_I	Inhalation biologically effective dose [mg/(kg-organ d)]
E_O	Oral biologically effective dose [mg/(kg-organ d)]
G_v	Guideline value (mg/L)
K_{mk}	Michaelis constant for enzymatic reaction for the kidneys (mg/L)
K_{ml}	Michaelis constant for enzymatic reaction for the liver (mg/L)
K_p	Effective skin permeability coefficient (cm/d)
$I_{food,i,j}(r)$ [1)]	Daily intake of j^{th} food in i^{th} food group (g/d)
I_{water}	Daily drinking water consumption (L/d)
P_{ba}	Blood/air partition coefficient (dimensionless)
P_{fb}	Fat/blood partition coefficient (dimensionless)
P_{kb}	Kidney/blood partition coefficient (dimensionless)
P_{lb}	Liver/blood partition coefficient (dimensionless)
P_{rb}	Rapidly perfused /blood partition coefficient (dimensionless)
P_{sb}	Slowly perfused /blood partition coefficient (dimensionless)
P_{skb}	Skin/blood partition coefficient (dimensionless)
P_{skw}	Skin/water partition coefficient (dimensionless)
Q	Breathing rate (L/d)
Q_{alv}	Alveolar ventilation rate (L/d)
Q_f	Blood flow rate to fat (L/d)
Q_k	Blood flow rate to the kidneys (L/d)
Q_l	Blood flow rate to the liver (L/d)
Q_r	Blood flow rate to rapidly perfused tissues (L/d)
Q_s	Blood flow rate to slowly perfused tissues (L/d)

Q_{sk}	Blood flow rate to skin (L/d)
Q_t	Cardiac output (L/d)
t	Time (d)
$t_{bathroom}(r)$ [1)]	Time spent in bathroom per day (dimensionless)
$t_{kitchen}(r)$ [1)]	Time spent in kitchen per day (dimensionless)
$t_{residence}(r)$ [1)]	Time spent in residence per day (dimensionless)
$t_{outdoor}(r)$ [1)]	Time spent outdoors per day (dimensionless)
V_f	Volume of fat (L)
V_l	Volume of the liver (L)
V_k	Volume of the kidneys (L)
V_{maxl}	Maximum enzymatic reaction rate for the liver (mg/d)
V_{maxk}	Maximum enzymatic reaction rate for the kidneys (mg/d)
V_r	Volume of rapidly perfused tissues (L)
V_s	Volume of slowly perfused tissues (L)
V_{sk}	Volume of skin (L)
α	Ratio of effective doses by single/continuous exposure (dimensionless)
α_1	Ratio of oral effective doses by single/continuous exposure (dimensionless)
α_2	Ratio of inhalation effective doses by single/continuous exposure (dimensionless)
α_3	Ratio of dermal effective doses by single/continuous exposure (dimensionless)
$\alpha_{2/1}$	Ratio of α_2 to α_1 (dimensionless)
$\alpha_{3/1}$	Ratio of α_3 to α_1 (dimensionless)
β	Ratio of effective/potential dose at a constant continuous administration (kg-body d/kg-organ)
β_1	Ratio of oral effective/potential dose at a constant continuous administration (kg-body d/kg-organ)
β_2	Ratio of inhalation effective/potential dose at a constant continuous administration (kg-body d/kg-organ)
β_3	Ratio of dermal effective/potential dose at a constant continuous administration (kg-body d/kg-organ)
$\beta_{2/1}$	Ratio of β_2 to β_1 (dimensionless)
$\beta_{3/1}$	Ratio of β_3 to β_1 (dimensionless)
ϕ	Ratio of alveolar ventilation rate to breathing rate (dimensionless)

1) "(r)" indicates Monte-Carlo input.

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Supplementary Information C

Monte-Carlo and multi-exposure assessment for the derivation of criteria for disinfection byproducts and volatile organic compounds in drinking water: allocation factors and liter-equivalents per day

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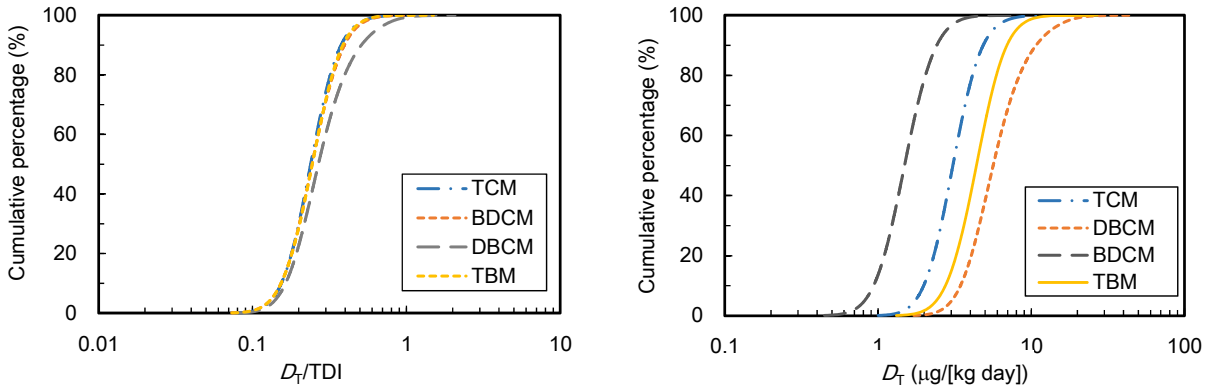

Fig. SC1. The probability density function of the total oral-equivalent potential dose (D_T) for TCM (60 μg/L), BDCM (30 μg/L), DBCM (100 μg/L), and TBM (90 μg/L) in drinking water (these concentrations are equal to the corresponding DWQS values).

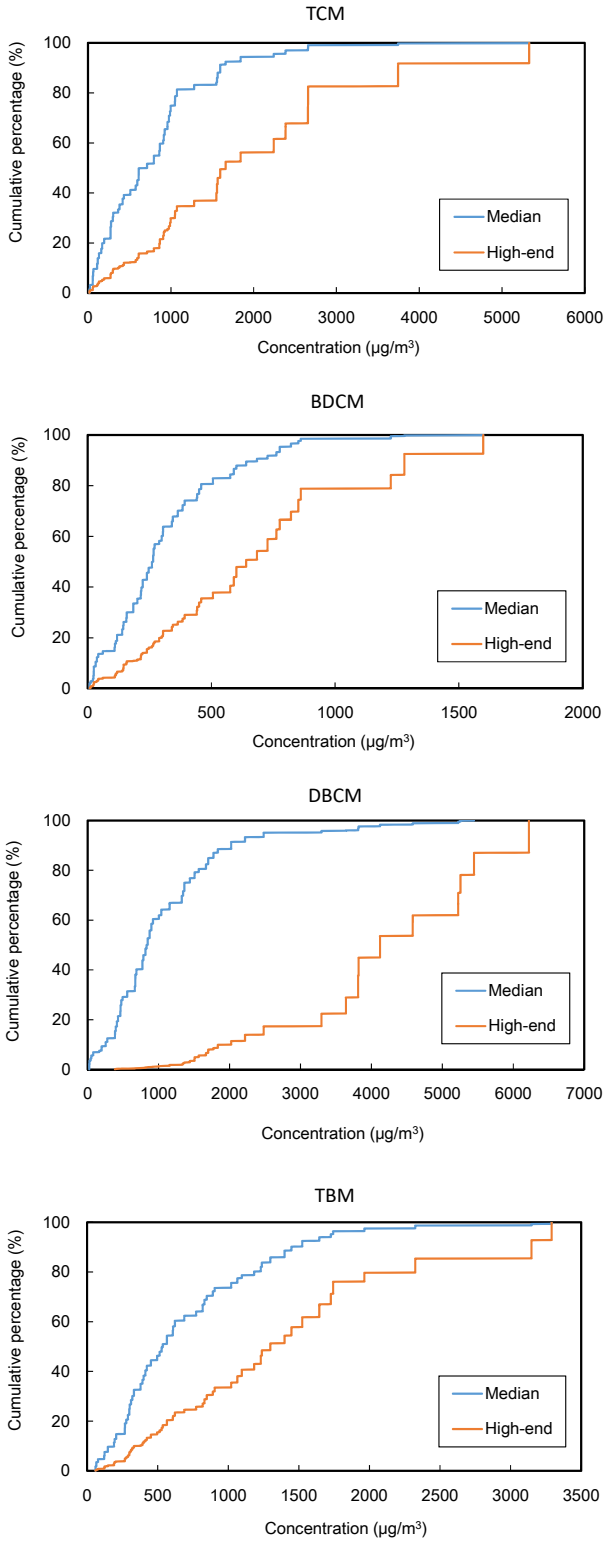

Fig. SC2. Cumulative probability of concentrations of DBCM and TBM in inhaled air in a bathroom for two subpopulations. The orange line represents the high-end exposure population (the 95th percentile population, total oral-equivalent potential dose = TDI). The blue line represents the median exposure population.

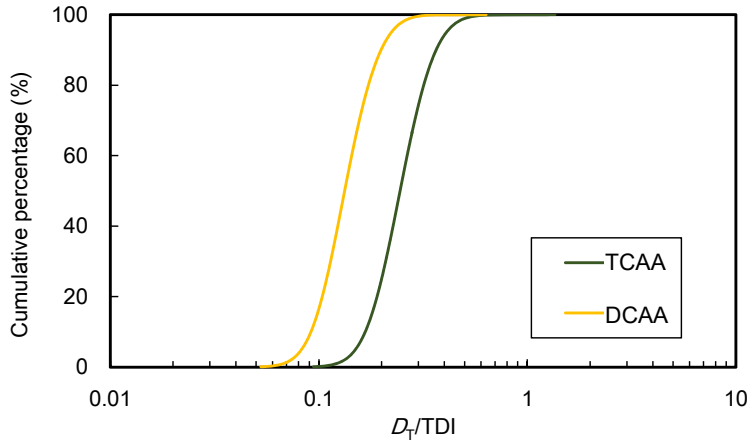

Fig. SC3. The probability density function of the total oral-equivalent potential dose of TCA and DCA when the concentration in drinking water is equal to the corresponding DWQS value.

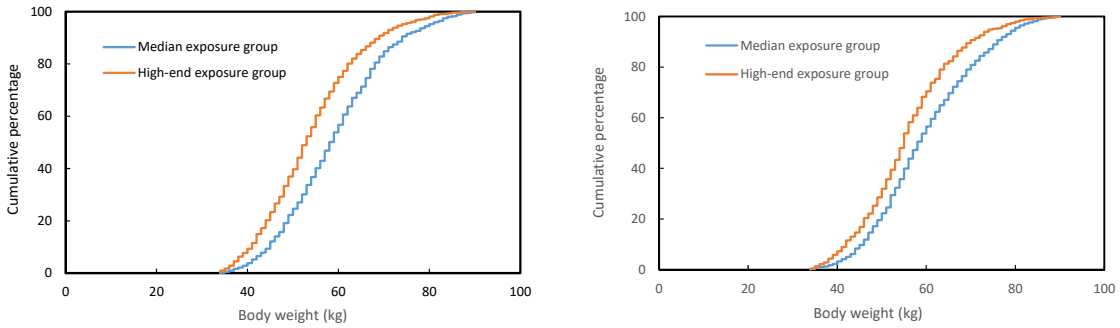

Fig. SC4. Body weight distributions of the high-end exposure group and median exposure group for HAAs.

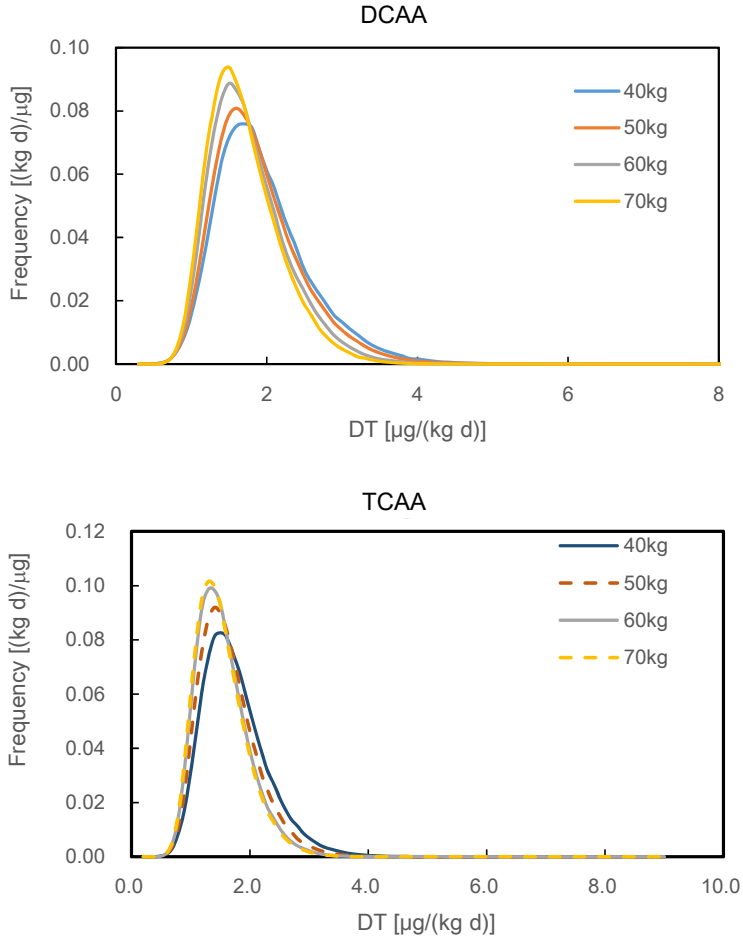

Fig. SC5. Effect of body weight on the probability density function of the total oral-equivalent potential dose of DCAA and TCAA.

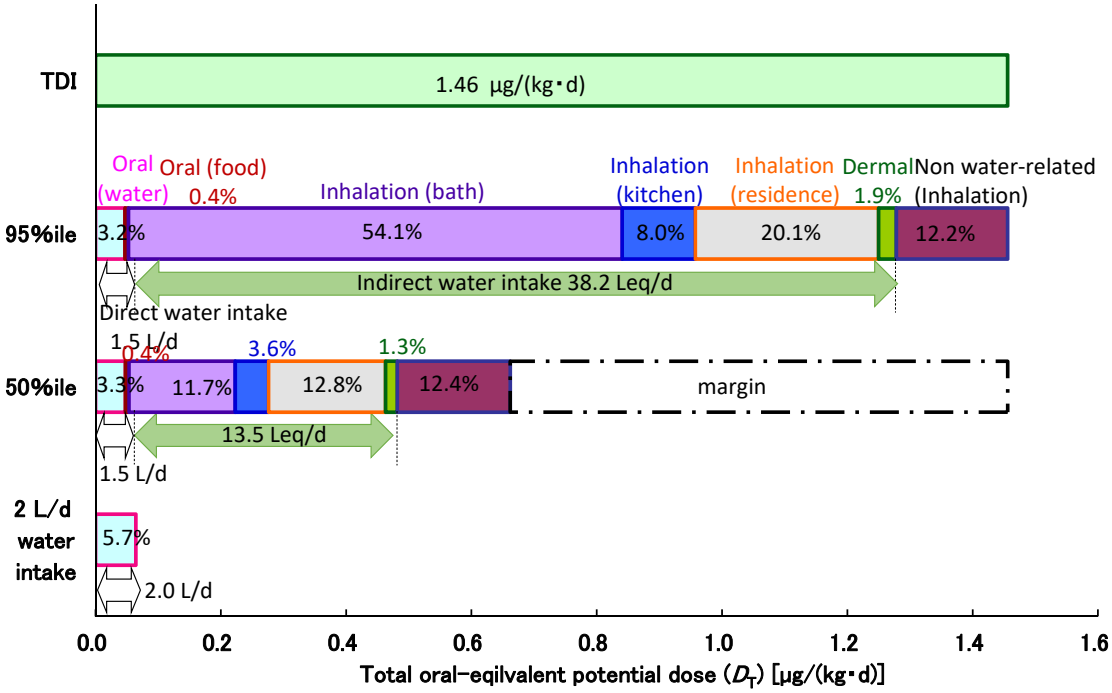

Fig. SC6. Total oral-equivalent potential doses of TCE and its breakdown products when the 95th percentile estimates were equal to the corresponding TDIs. The TCE concentrations in drinking water were equal to 1.6 μg/L. The second and third bars shows the median (50th percentile) and the 95th percentile estimates, respectively. The $R_{2/1}$ value of 2.24, which was estimated for the plasma concentration of TCE as a dose metrics, was used.

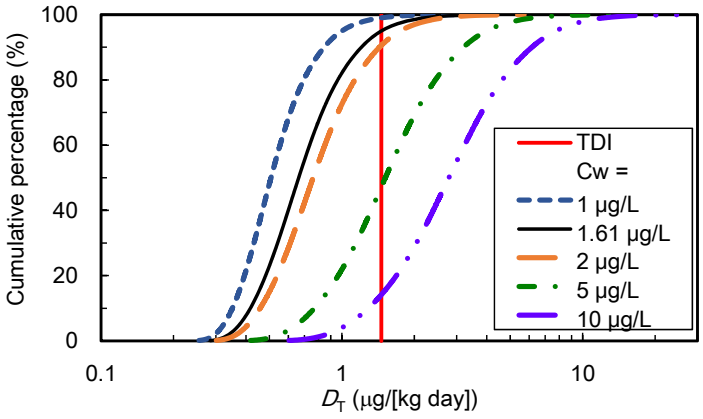

Fig. SC7. The probability density functions of the total oral-equivalent potential dose of TCE when concentration in drinking water (C_W) are 1, 2, 5 and 10 μg/L. The red lines indicates TDIs of TCE and PCE. The $R_{2/1}$ value of 2.239, which was estimated for the plasma concentration of TCE as a dose metrics, was used.