An assessment of non-occupational 1,4-dioxane exposure pathways from drinking water and product use

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Supplemental Information S1

S1.1. Appropriateness of SHEDS-HT to 1,4 Dioxane and General Applicability of Workflow to other Chemicals

1,4-Dioxane exposure was estimated through ingestion, inhalation, and dermal pathways in this study with SHEDS-HT. One issue of concern is the suitability of the SHEDS-HT exposure modules to 1,4 dioxane. SHEDS-HT was designed from the SHEDS "family" of exposure models to be applicable to a wide variety of chemicals, particularly chemicals contained in consumer products (see section S7 for greater detail). It's exposure and absorption equations are generic (S2.2) and vary by pathway. However, most are mechanistic and utilize both physiological information, derived from model-based and empirical sources, and chemical properties, estimated from 5 sources: USEPA's EPI Suite[1], the OPERA suite of models[2], a model predicting dermal permeability[3] , and a model predicting the fraction absorbed in the gut [4]. See Supplemental Information S2.1 for pathway-specific equations. In the sections below, we discuss

the general applicability of the methodology for each exposure route used by SHEDS-HT and compare the exposure conditions used here versus the US EPA(2020)[5] in their Final Risk Evaluation for 1,4 Dioxane. Lastly, we discuss the general applicability of the workflow to other chemicals,

S1.1.1. Ingestion

The equations used in SHEDS-HT to estimate exposure via ingestion are similar to those used by the US EPA (2020)[5]. Where the EPA (2020) evaluation implicitly assumes 100% absorbance of 1,4-dioxane through the gut, SHEDS-HT uses a QSAR model to predict absorbance[4]. 1,4-Dioxane appears to be well within the domain of this model, with the prediction (97%) similar to that suggested by rat studies[6]. In our study, exposure from ingestion occurred through drinking water and hand-to-mouth transfer while US EPA (2020) only assumed incidental ingestion during swimming in surface waters near industrial release points. Thus, exposure conditions significant differed between the two studies, with the latter study focusing on high exposure scenarios.

S1.1.2 Inhalation

SHEDS-HT uses a set of equations to model aggregate inhalation exposure from direct exposure to chemicals in products (See Supplemental S2.1) over a 1-day period. It combines

information on use factors (use duration, product mass, room size), chemical characteristics (vapor pressure), and physiological/activity characteristics (ventilation rate, physical activity) to stochastically calculate exposure. It currently employs a generic absorbance function that assumes (based on legacy reasons) a static 16% of exposed chemical absorbed through the lungs. Research into inhalation exposure of 1,4 dioxane suggests that absorption via inhalation may be closer to 50%[7]. However, in contrast to our study in which exposure is via 1,4 dioxane dissolved in products, Goen et al. (2016) [7] exposed humans to evaporated 1,4 dioxane within an environmental chamber. To evaluate the impact of this assumption, additional ad hoc simulations with an assumed fraction absorbed through inhalation set at 0.5 resulted were run, with all other settings the same as the full factorial simulations. These simulations resulted in increases in human exposures relative to the default SHEDS-HT inhalation boundary, ranging from 22-88% for the Both population, 167-440% for the Products-Only population, and 132-426 % for the Total population. It resulted in relatively small changes in the proportions attributable to water ingestion compared to the default value, ranging from differences of 5.6% to decreases of 27%, relative to the lower fraction absorbed through inhalation assumption. The biggest differences in the proportion of human exposure attributable to water ingestion occurred in people with surface

water and a low $Prevalence_{products}$ assumption. This is because surface water had the lowest 1,4 dioxane concentration, and thus would be more influenced by changes in product contributions to exposure. The two assumed fractions absorbed (16% & 50%) likely represent lower and upper bounds which require additional experimental work to clarify. See Supplemental Information 2.10 for the outputs from these ad hoc simulations.

The equations used in SHEDS-HT to estimate inhalation exposure are similar to those used by US EPA (2020)[5] to calculate occupational exposure to 1,4-dioxane. In contrast, to estimate exposure from products US EPA(2020) used the Consumer Exposure Model (CEM)[8], a deterministic mass-balance model, to calculates 8 hour time-weighted averages over a 72 hour exposure window for high and median intensity users. The exposure equations of this model are functionally similar to those employed in SHEDS-HT, but much greater detail is used in calculating exposure concentrations in different compartments of the interior space over time. SHEDS-HT does have a fugacity model built into its indirect inhalation exposure module with similar functionality. However, that module was not used here as the products considered are washed down the drain shortly after their use. Therefore, SHEDS-HT provides a more simplistic snapshot of inhalation exposure than the methods employed by US EPA (2020), but it provides a

distribution of aggregate estimates instead of point estimates of median to high exposures from each product.

S1.1.3. Dermal exposure

SHEDS-HT combines information on use factors (use duration, product mass) and chemical characteristics (dermal permeability, dermal absorbed fraction) to calculate dermal exposure, and accounts for the quantity of chemical removed through handwashing, bathing, wipe-off, and hand-to-mouth actions. The fraction of 1,4-dioxane exposure absorbed dermally may be relatively minor, with available studies limited to one involving excised human skin (0.3-3.2%), and an *in vivo* study involving monkey skin (<4%). SHEDS-HT estimates dermal absorption by multiplying an absorbed fraction randomly sampled from a triangle distribution (0.001,0.01, 0.004) by the Kp of the chemical (scaled by the Kp for permethrin [9]). Then, this value is multiplied by the amount of dermal exposure remaining after handwashing, bathing, being brushoff, and transferred hand to mouth. This results in a very low proportion of dermal exposure is estimated to be absorbed by SHEDS-HT (≈0.001%). However, the products included in our analyses are not intended to be left on the skin, as chemicals in the above experiments were. US EPA (2020) estimated exposure via a dermal pathway from swimming and product use. The underlying exposure equations used by US EPA(2020) to estimate dermal exposure

during swimming was similar to the approach used by SHEDS-HT, but the approach used to estimate dermal exposure through consumer product use utilized the mass-balance model of the CEM. This method entailed a more nuanced approach to fraction absorbed than utilized in SHEDS-HT. Therefore, as for inhalation above, SHEDS-HT provides a more simplistic snapshot of dermal exposure than US EPA (2020), but it provides a distribution of aggregate exposure estimates instead of a range of median to high point estimates from exposure to each product. Finally, SHEDS-HT does not consider dermal exposure from swimming at all.

S1.2 Data for exposure pathways

S1.2.1 Drinking Water Data

Parameters for the tap water pathway through ingestion included 1,4 dioxane concentration and prevalence of 1,4 dioxane contamination in tap water ($prevalence_{water}$), and the amount of tap water ingested. The parameters for mass released DTD from water included the average aggregate amount of tap water use per household. First, concentrations of 1,4 dioxane in drinking water were obtained from the UCMR3[10], collected from 2013-2015 at a subset of public drinking water systems across the United States. $Prevalence_{water}$ by source (groundwater, surface, mixed) was determined on a population basis; that is, $prevalence_{water}$ was defined as the proportion of the population served by systems where 1,4 dioxane was detected above the

minimum detection limit. Total populations served by water systems listed in the UCMR3 sample were ascertained by linking this dataset with the USEPA Safe Drinking Water Information System (SDWIS) dataset by water system ID's (i.e., PWSID). It is likely that non-detects of 1,4 dioxane in UCMR3 samples do not equate to concentration = 0 (i.e., water not contaminated), but rather to some value less than the minimum detection level of the analytical method (0.02 ug/L[11]). However, to facilitate the comparison of different subpopulations based on exposure or not to contaminated water (see Section 2.5 for additional details), we assume here that a non-detect for water contamination is equal to 0 ug/L.

Total water ingested included water consumed directly, as well as through drinking water incorporated into food. This information was derived from the NHANES What-We-Eat-in-America (WWEIA)[12] study conducted from 2009-2019. Food diaries were downloaded for each NHANES cycle (F-J). The data files contained recall diary information describing the foods and beverages consumed by study participants in all eating occasions in the 24-hour period (midnight to midnight) prior to the interview. Two separate days of recall data were reported for most individuals; data from the two days were treated as independent. Total moisture W_{Tot} (in ml) in each food item consumed was reported in the file (as variables DR1IMOIS and DR2IMOIS for

day 1 and day 2 of the study, respectively). A subset of NHANES food codes assumed to contain tap water were identified (including directly consumed tap water, packaged foods, and drinks prepared with tap water) by searching for the word "water" in the description, and manually verifying that the description described the addition of water to the food. Each of these foods were assigned a fraction f assumed equal to the fraction of total moisture in the food item that could be attributed to tap water. All foods not containing tap water were assigned f=0. This process was made according to empirical information when available, and otherwise used reasonable assumed values. Per capita daily tap water consumption (mL) was then calculated by multiplying the moisture content of the food type by the proportion of tap water for each food type and summing over all foods. This value was added to the total mL of direct drinking water consumption to obtain a value for the total drinking water consumed per day. This information was provided as a customized food diary input file to SHEDS-HT.

Mass released DTD estimates from drinking water were made using gross per capita water usage data from the USGS[13]. Included implicitly were quantities for major contributing activities such as bathing, handwashing, dishes, and laundry. Per capita quantities of water ingested as drinking water based on NHANES data were a very small proportion of average

daily water usage in the US (<1%) and was not subtracted from the gross total considered for mass released DTD. Water used in outside applications such as lawn watering would not be expected to be captured by WWTPs. Though averaging nationally up to 30% of domestic water use[14], lawn watering would be expected to be vary by factors beyond the granularity of this analysis, including regional variation[15] and whether people are homeowners are renters. Thus, we ignore the influence of lawn watering on down the drain calculations here.

S1.2.2 Consumer Product Data

For human exposure from product use, we considered six product classes: shampoo, body wash, hand soap, laundry detergent, manual dish detergent, and bubble bath. Concentrations of 1,4 dioxane in these consumer products were estimated from three different sources, including a primary literature source[16], and two consumer advocacy organizations[17, 18]. The product classes selected for inclusion here were those that were identified by these sources as consistently having detectable levels of 1,4 dioxane. In contrast, products such as hair conditioner and lotions were generally not found to contain 1,4 dioxane. In all cases, concentration of 1,4 dioxane in samples of consumer products was estimated using Gas Chromatography with Mass Spectrometry (GC/MS). In the case of two sources (Zhou et al. (2019), Sarantis et al.(2009) [17, 18]), independent

laboratories provided blind analytical determination of samples (using Method 8260C or similar). See Supplemental Information (S2.1) to see the assembled consumer product data.

As required by SHEDS-HT, mean 1,4 dioxane concentrations (listed in ug/L) per product category of interest were converted to weight fractions, and coefficients of variation were calculated. We explicitly considered a range of values for chemical prevalence in products ($Prevalence_{products}$) as part of our factorial analyses; see section 2.4.1 below for more details. Product usage parameters (frequency of use, prevalence of use, duration of use, etc.) utilized included either default values in SHEDS-HT (which include a mix of primary literature and reported values), or they were from the Exposure Factors Handbook[19]. Please see the Supplemental Information (S3) for a listing of sources for each parameter.

S1.3. Modifications to Default SHEDS-HT

Three main adjustments were made to the default SHEDS-HT coding of the dermal and DTD modules to improve realism and better match the assumptions exposure scenarios. First, we linked the exposure and DTD processes to ensure that the concentrations of 1,4 dioxane in drinking water exposures for a particular person matched those used in making mass released DTD estimates for that person. Next, by default SHEDS-HT selects the frequency of

handwashing and bathing, which reduce exposure to chemicals via the dermal pathway, independently of product use for a person. However, some of the products considered here are associated with handwashing (i.e., hand- soap) and bathing (i.e., shampoo, bubble bath, bodywash). To accommodate this connection, we set the number of handwashing events to be at least as many as uses of hand-soap, and the number of bathing events to be at least as many as the usage events of shampoo, bubble bath or body wash. In this way, a person could wash their hands and/or bath without using the corresponding product, but not the converse.

Lastly, by default SHEDS-HT assumes independence in the probabilities of using each product. This independence is useful in a high throughput scenario with multiple chemicals and products, and when conservative estimates of aggregate chemical exposures are desired. However, when a subset of specific products is utilized, it can result in unlikely scenarios that overestimate product use and exposure. For example, a person could be assigned to use multiple kinds of laundry detergent (gel, liquid, other) or shampoo on the same day. To more realistically estimate product use, similar product types (e.g., dish detergent, laundry detergent, shampoo) were clustered, creating simple dependence between types. This was done by considering two scenarios. In the first, multiple subtypes of a product (e.g., laundry detergent(e.g., powder vs

liquid) exist, but only one of these is likely to be used by a person in day. In this case, a single subtype is first selected for a given person based on assigned weight. Then, a Bernoulli trial is run to determine whether or not the person uses the product on the day. Because we did not have market penetration information, all such subtypes were equally weighted (e.g., selection probability for 1 of 3 subtypes =0.333). As a result, the product use prevalence parameter in this situation is considered the probability of using a product subtype given that a product type is selected.

In the second scenario, one or more of the product types is considered a sub-product of another. For example, shampoo may be classified as just "shampoo" or "dandruff shampoo". So, dandruff shampoo is a subset of shampoo of the overall product type. However, while 100% of people are assumed to use shampoo, only about 10% of people are assumed to use dandruff shampoo, and it is unlikely that people would use both dandruff and non-dandruff shampoo on the same day. To handle this situation, the use of the overall product (e.g., shampoo) on a given day is assigned first. Then, the proportion of people using the subtype on that day are assigned from the people assigned to use the general type.

S1.4. SHEDS-HT Parameter Estimation.

SHEDS-HT uses a Monte Carlo approach to assign parameter values determining exposure estimates. This is accomplished by sampling from distributions based on user-input arithmetic means and coefficient of variations (CV) for each parameter. SHEDS-HT currently allows the user to specify one of 3 distribution types for each parameter, including the normal, lognormal, and Bernoulli distributions. The lognormal distribution is commonly used in exposure research and, like the normal distribution, tends to be appropriate when looking at the distributions of many independent observations. Bernoulli distributions are utilized for point estimates and represent parameters for which there is limited knowledge of uncertainty. To choose whether normal or lognormal distributions were more appropriate for parameters for which a collection of data points existed, we used the fitdistrplus package[20] in R to fit data to those distributions. We then calculated the Akaike Information Criterion (AIC) value for each fit, and chose the distribution for the lower of the two fits for each parameter. The distribution assigned to is listed in the Supplemental Information (S3).

S1.5. Estimating prevalence of 1,4 Dioxane from list of proxy ethoxylated chemicals

One of the 3 factors we used in the analyses was $prevalence_{products}$, the prevalence of 1,4 dioxane in different consumer product classes. SHEDS-HT expects a point estimate for prevalence that it uses as a probability in a Bernoulli trial to determine if a chemical is present in a product. However, there is inherent uncertainty in determining $prevalence_{products}$, as it depends upon the specific products in each product class considered, as well as the market penetration of those products. We explicitly accounted for this uncertainty by using a low-high bounding approach. In the consumer advocacy studies of 1,4 dioxane in consumer products used here to estimate concentrations of 1,4 dioxane in product classes[17, 18], the $prevalence_{products}$ within samples may be biased high because the organizations conducting that research may have been seeking products with ethoxylated ingredients. Thus, the prevalence information from these sources served as a high bounding estimate. This was calculated as the number of products in a given class (e.g., shampoo) with 1,4 dioxane detections, divided by the total number of products sampled in that class. See Supplemental Information (S2.1) for assembled consumer product concentrations used in this calculation.

To determine a lower bound of $prevalence_{products}$, we assembled a list of ethoxylated chemicals expected to be found in consumer products, cross-referenced the list with a consumer

product database, and then calculated a $prevalence_{products}$ based on the proportion of products found in each product class containing at least chemical from the proxy list. To start this process, we first assembled a list of 335 ethoxylated chemicals from two sources: the Mintel Database,[21] and the American Cleaning Institute's Cleaning Product Ingredient Inventory.[22] Ethoxylated chemical ingredients in the list were exported as a search list from Mintel, and then identified in the ACI Cleaning Product Ingredient Inventory by expert chemist review. Next, we cross referenced the CAS Registry Numbers (CASRN) and common names of the chemicals on the list to chemical DTXSIDs listed on the USEPA Comptox Dashboard,[23] where possible. Of the 335 chemical names checked in this manner, 116 unique chemicals were recognized by the dashboard. For each chemical a list of synonyms used in ingredient descriptions was identified using the CompTox Dashboard. Next, we cross-referenced the list of synonyms with products (in the product classes of interest) downloaded from the EPA Chemical and Products database[24] (CPDat), a database of consumer products and their ingredients constructed from information made available on MSDS sheets. Lower bound $prevalence_{products}$ calculations (See Supplementary Information (S2.3)) were then made by determining the proportion number of chemicals in each product class containing at least one of the chemicals in the chemical proxy list. For example, if 10 of 20 products in a product class contained at least 1 of the chemicals, the

$prevalence_{products}$ would be considered 0.5. In the case where the lower bounding estimate exceeded the high bounding estimate (in the case of laundry detergent), the highest available prevalence value was used for both.

S1.6. Projecting down-the-drain exposure to wastewater concentrations

To translate down-the-drain (DTD) exposure predictions from SHEDS-HT to expected wastewater loading, we used the web-based ISTREEM tool[25]. This freely available tool is currently hosted by the American Cleaning Institute and predicts concentrations of chemicals at WWTPs (influent and effluent) and drinking water intakes across the US as a function of user-specified per capita DTD concentrations. Using this tool, we predicted expected concentrations (µg/L) of dioxane in wastewater effluent at 142 WWTPs in CA (reported to serve 1,422,830 people) and 13,245 WWTPs in the US (reported to serve 18,2615,938 people) overall. This accounts for 36% and 55% of the populations of the US and CA, respectively. Though advanced methods have been developed to reduce dioxane in some circumstances and localities[26], standard wastewater treatment does not appreciably reduce dioxane concentration[27]. So, only a single concentration influent/effluent (WWconc) was calculated per plant using the following equation:

$$WWconc = \left(\frac{PopulationServed * DTD_{g/day}}{FlowRate_{MGD} * 3785411.8_{LPD/MGD}}\right) * 1x10^{6}{}_{\mu g/g}$$

Is this equation, $PopulationServed$ and $FlowRate_{MGD}$ are the total population and flow rate (in millions of gallons per day), respectively, for a given wastewater system as indicated by ISTREEM. $DTD_{g/day}$ is the mean DTD estimate for a factorial combination of *scale*, water *source*, and $prevalence_{products}$. The two constants convert flow rate in MGD to liters per day and dioxane concentrations from g/l to ug/l. Finally, we compared the predicted means and 95% effluent concentrations for each factorial combination to the corresponding US or CA-scale WWTP dioxane concentrations.

S1.7 General applicability of workflow

The work developed to carry out the described analysis of this study consists of several R-scripts, a single "master" MS Excel workbook containing all of the input files needed to run SHEDS-HT, and a version of the SHEDS-HT R package with study-specific modifications (see S1.5). This workflow (available on GitHub) is contained within a folder with nested directories, making the results of this study straightforward to replicate and modify. In addition, the master input file makes it relatively straight-forward to modify simulation parameterizations for additional modeling scenarios. In contrast, the manual assembly of data is not easily replicable.

A workflow situated within an integrative data environment, such as a bridged life cycle analysis-exposure ontological framework[28, 29] that utilizes exposure and life-cycle databases, would be ostensibly faster and easier to implement. Thus, it may be desirable for future iterations or versions of this workflow to utilize such an approach to data assembly.

For other chemical classes of interest, pathway specific absorption may be insufficiently captured by the current version of SHEDS-HT, either due to inaccurate chemical properties information, or insufficiently complex exposure/absorption relationships. In an example of the former, chemicals with amphiphilic properties (e.g. PFAS) may lie outside the applicability domain of the model predicting ingestion fraction[4], making absorption predictions unreliable. In an example of the latter, absorption of chemicals that rely upon transporters (e.g., many pharmaceuticals) also may be misestimated. However, because SHEDS-HT models exposure through mechanistic equations (S2.1), exposure estimates could be coupled with more chemical or chemical-class specific absorption functions post-hoc. This would allow for the bulk of the workflow to be retained, and thus generally useful for a variety of exposure scenarios. In addition, for functions such as the inhalation absorption fraction, the single assumed value could be replaced with values predicted from QSAR or read-across methods.

Additional Material:

The portable workflow for this project is freely available at BitBucket at:

https://bitbucket.org/DanielDawsonEPA/dioxane_portable_exposure_workflow/src/master/

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