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Stochastic modeling of near-field exposure to parabens in personal care products

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23

Abstract

Exposure assessment is a key step in determining risks to chemicals in consumer goods including personal care products (PCPs). Exposure models can be used to estimate exposures to chemicals in the absence of biomonitoring data and as tools in chemical risk prioritization and screening. We apply a PCP exposure model based on the product intake fraction (PiF), which is defined as the fraction of chemical in a product that is taken in by the exposed population, to estimate chemical intake based on physicochemical properties and PCP usage characteristics. The PiF can be used to estimate route and pathway specific exposures during both the use- and disposal-stages of a product. As a case study, we stochastically quantified population level exposures to parabens in PCPs, and compared estimates to biomarker values. We estimated exposure based on the usage of PCPs in the female US population, taking into account population variability, product usage characteristics, paraben occurrence in PCPs, and the PiF. Intakes were converted to urine levels and compared to NHANES (National Health and Nutrition Examination Survey) biomonitoring data. Results suggest that for parabens, chemical exposure during product use is substantially larger than environmentally mediated exposure after product disposal. Modeled urine concentrations reflect well the NHANES variation of three orders of magnitude across parabens for the 50th, 75th, 90th, and 95th percentiles and were generally in good agreement with measurements, when taking uncertainty into account. This study presents an approach to estimate multi-pathway exposure to chemicals in PCPs and can be used as a tool within exposure based screening of chemicals as well in higher tier exposure estimates.

48

1. Introduction

49

50   In order to inform risk assessment of chemicals in cosmetics and personal care products

51   (PCPs) an understanding of individual and population level exposure is required.[1,2] The need for

52   exposure estimates based on various chemical uses is highlighted by the recent advances in high-

53   throughput exposure models for chemical prioritization[3,4] which can also be combined with high-

54   throughput toxicity estimates to inform risk.[5,6] Historically, these modeling efforts have focused

55   on far-field environmentally mediated exposures and less on near-field pathway exposures

56   occurring indoors and during product use.[3,7] Usage of PCPs has been shown to be well correlated

57   with exposure[8,9] and use-phase exposure has been estimated to be greater than environmentally

58   mediated exposure.[10,11] Modeling techniques can be used to estimate near-field and use-phase

59   exposures to chemicals in PCPs and can be used to further enhance chemical prioritization

60   methods for chemicals in consumer products.[6]

61   Several calculations have been developed to estimate chemical intake via PCP use and are

62   based on multiplicative models[1,2,12] using a set skin permeation fraction often derived from the

63   literature and do not necessarily take exposure duration (e.g. rinse-off versus leave-on into

64   account).[1] On the other hand, models have been developed to estimate the skin permeation

65   coefficient of a chemical[13,14] and chemical uptake into the skin.[15,16] Skin permeation models

66   provide the advantage that they can be applied to chemicals based on physicochemical properties

67   (i.e. octanol-water partition coefficient, K_{ow}, and molecular weight) thereby lending themselves

68   to computationally based calculations rather than relying on data from the literature which is not

69   conducive to multiple chemical calculations. Furthermore, models used to estimate exposure to

70   chemicals applied dermally vary in mathematical complexity, for example by assuming only one

71   chemical fate pathway (i.e. dermal uptake),[15] or only providing complex numerical solutions.[16]

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72   Modeling frameworks are currently being developed to combine dermal uptake with the concept

73   of the *product intake fraction*, PiF, defined as the fraction of the chemical in a product that is

74   eventually taken in by the exposed individual(s)/population.[17] These models can be applied to

75   predict chemical intake via several different pathways such as dermal uptake, inhalation intake

76   and gaseous dermal uptake of volatilized chemicals, and to environmentally mediated exposure

77   after product disposal. The advantage of this multi-pathway approach is that the relative

78   contribution of each pathway can be estimated and does not assume that exposure only occurs

79   via dermal uptake of product applied to the skin and allows for comparison between use-phase

80   and disposal-phase exposures.

81   Such models, however, have yet to be evaluated on a population level using for example,

82   biomarker data. Additionally, exposure is often estimated based on the usage of a single product

83   rather than an aggregate analysis taking into account usage of multiple products containing a

84   given chemical[1,2,15], which may underestimate a consumer's entire exposure for chemicals found

85   in multiple product types. Cowan-Ellsberry and Robison[1] and Gosens et al.[2] present aggregate

86   exposure estimates for parabens in PCPs, however their estimates do not use a skin permeation

87   model nor are their estimates validated against biomarker data. Delmaar et al.[15] estimated

88   aggregate exposure to diethyl phthalate using a skin permeation model, however they only

89   consider the dermal exposure pathway. The application of a multi-pathway exposure model to

90   estimate cosmetic intake has not been validated on a population level nor applied across multiple

91   product types to yield aggregate exposure estimates. To address this gap, the product intake

92   fraction concept would need to be adapted to several PCPs and validated against population level

93   data. Evaluation of a PCP exposure model using data rich chemicals will build further

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94   confidence in these techniques such that they can be incorporated into Tier 1 exposure and risk

95   screening approaches and used on a broader range of chemicals.

96   In this paper, we apply the PiF concept to model chemical intake due to PCP usage using

97   parabens as a case study. In order to compare the estimated intakes to population-based

98   biomonitoring data we probabilistically combined the PiF calculations with aggregate exposure

99   considerations to capture population variability, focusing on a class of widely used chemicals.

100   This type of analysis is referred to as a Tier 2 probabilistic exposure estimate[18] and is more

101   detailed than point estimates often used in screening approaches (Tier 1).[6] Parabens are

102   commonly used in PCPs and cosmetics as preservatives, are readily absorbed into the skin,[19] are

103   detectable in urine,[20] and thereby provide a good PCP exposure case study. Urinary biomarker

104   data is available for the US population from NHANES (National Health and Nutrition

105   Examination Survey)[21] where parabens have been detected in ~99% of the population.[22]

106   Additionally, parabens are suspected endocrine disruptors[23,24] and these exposure calculations

107   provide a basis for informing risk when combined with toxicity, bioactivity, or allowable dose

108   data.[17] This study therefore aims to:

109   1. Estimate and contrast modeled *product intake fraction* for various exposure pathways

110   (including near and far-field exposures) for parabens in a variety of PCPs and cosmetics

111   while accounting for both chemical specific properties and product use characteristics.

112   2. Develop a stochastic method to produce population distributions of exposure resulting

113   from the usage of multiple PCPs.

114   3. Evaluate the stochastic method by comparing its predictions with NHANES urine

115   concentrations at different percentiles (50th to 95th) of exposure in the US population.

116   **2. Methods**

117   We used four common parabens methyl, ethyl, propyl, and butyl paraben (MeP, EtP, PrP,

118   BuP, respectively) and eleven commonly used personal care products (PCPs) as a case study. We

119   included rinse-off products (shampoo, conditioner, facial cleanser, body wash) and leave-on

120   products (body lotion, face cream, night cream, deodorant, foundation, eye shadow, and lipstick).

121   We studied the U.S. female population due to the availability of urine biomarker data[21] and the

122   significantly higher exposure of the female versus male population to parabens.[22]

123   *2.1 Product Intake Fraction*

124   We used the product intake fraction (PiF) metric to assess the fraction of parabens in

125   products that humans are exposed to a) during product use and b) via subsequent environmental

126   emissions after product use. The PiF is defined as the ratio of the amount of chemical in a

127   product that is taken in by humans and the amount of chemical contained in that product and

128   depends on physicochemical properties as well as product use characteristics.[17] Once a product is

129   applied we assumed that it can undergo the following pathways: direct dermal uptake into the

130   skin, volatilization to air, and washed down-the-drain after the product is rinsed off. Following

131   from these pathways, we calculated a PiF for each of the following exposure pathways: dermal

132   uptake of chemical in an aqueous product ($PiF^{\text{derm,aq}}$), inhalation of chemical from the volatilized

133   product (PiF^{inh}), gaseous dermal uptake of chemical from the volatilized product ($PiF^{\text{derm,gas}}$),

134   and environmentally mediated chemical intake due to disposal after product use (PiF^{disp}), for

135   each paraben and each PCP type.

136   The expression for dermal uptake of chemicals in aqueous products into the skin ($PiF^{\text{derm,aq}}$)

137   is based on a two-compartment mass balance between product and skin and yields the following

138   solution (see Table S1 in Supplementary Information (SI)):

139
$$PiF^{\text{derm,aq}} = \frac{k_{\text{ps}}}{k_{\text{ps}} + k_{\text{pa}}}\left(1 - e^{-(k_{\text{ps}} + k_{\text{pa}})t}\right) \tag{1}$$

6

140   where k_{ps} (h^{-1}) and k_{pa} (h^{-1}) are the product-skin and product-air transfer rates, respectively and

141   t (h) is the exposure time, that is the duration that the product stays on the skin before being

142   washed-off. The transfer rates k_{ps} and k_{pa} are both functions of the thickness of product on the

143   skin, in addition to chemical specific parameters such as the aqueous skin permeation

144   coefficient, K_p^{aq} (cm h^{-1}) and the air-water partition coefficient (K_{aw}) respectively. Expressions for

145   the intake of volatilized chemical via inhalation (PiF^{inh}) and gaseous dermal uptake ($PiF^{derm,gas}$)

146   are given in SI, Table S1, and are summed with $PiF^{derm,aq}$ to constitute the total use-stage, PiF^{use},

147   via these exposure routes.

148   The PiF associated with product disposal, PiF^{disp} (SI, Table S1), was modeled as the fraction

149   of chemical not taken in during use and subsequently washed down the drain into a waste water

150   treatment plant (WWTP) and then released to environmental compartments (air, water, soil). The

151   subsequent environmental intake fractions (iF) were calculated using the USEtox model.[25]

152   Finally, a chemical and product specific PiF^{tot} can be defined as the sum of chemical intakes via

153   all considered pathways (i.e., $PiF^{derm,aq}$, $PiF^{derm,gas}$, PiF^{inh}, PiF^{disp}) and represents the total

154   chemical intake via all exposure routes. More details on the calculation of the various pathway

155   and route specific PiFs can be found in the SI (Section S1).

156   We note that some personal care products may also lead to non-dietary ingestion exposure,

157   for example mouthwash and toothpaste, however these products are not reported to contain

158   parabens[12,26] and were thus not included in the model. An ingestion PiF can be readily

159   incorporated into this modeling framework and can take the value of the fraction of product that

160   is ingested per product use. For example, for toothpaste Bremmer et al.[27] used measured values

161   to estimate a toothpaste ingestion fraction. We did not include an ingested fraction for lipstick as

162   the resulting median $PiF^{\text{derm,aq}}$ was already larger than 50% for all parabens, and previously

163   assumed fixed ingestion fractions for lipstick can vary greatly (e.g. from 0.1-100%).[4,27]

164   *2.2 Total daily intake*

165   The PiF^{tot} can then be used to calculate daily intake for a given chemical in a product and can

166   be summed across several different products (p) to calculate an aggregate chemical intake, I (mg

167   kg^{-1} d^{-1}) as

168     $$I = \frac{\sum\limits_{\text{p}} PiF_{\text{p}}^{\text{tot}} M_{\text{p}} f_{\text{p}}}{BW} \qquad (2)$$

169   where M_{p} (mg d^{-1}), f_p, and BW (kg) are the daily mass of product applied, fraction of chemical

170   in the product, and body weight, respectively.

171   *2.3 Monte Carlo Analysis, Model Parameterization, and Aggregate Exposure*

172   Several of the parameters used as input to model the intake of chemicals in PCPs are subject

173   to population variability, i.e. can have a range of possible values depending on individual

174   characteristics and behavior within the studied population. We used Monte Carlo (MC) analysis

175   to incorporate this population variability into our intake calculations. The parameters included in

176   the analysis as well as their distributions are listed in SI, Table S5. The MC analysis was carried

177   out for each product and chemical combination by generating 10^5 random values for each input

178   parameter from the given probability distribution and using these values to calculate an intake

179   distribution. Thus in total for four parabens in 11 PCPs yields 44 calculated intake distributions.

180   We note that the MC analysis considered variables to be independent and potential impacts of

181   variable correlations were not assessed.

182   Several key parameters dictate the calculated PiF and intake for a given product-chemical

183   combination and include the aqueous skin permeation coefficient, K_{p}^{aq}, the daily amount of

184   product used, M_{p}, and the fraction of chemical in the product, f_{p} (Eq. 2). We collected

185   empirical values of $K_{\mathrm{p}}^{\mathrm{aq}}$ for parabens conducted in different media such as an aqueous solution

186   or with an added alcohol and based the input distribution on these values[28–33] (Table 1 and S3).

187   For the daily mass of product usage, we used distribution data from Loretz et al.[34–36] as these

188   data pertain specifically to the U.S. female population and detailed information on distributions

189   were available for the MC analysis. Generally, there is limited information available on the

190   chemical composition of consumer products, including PCPs.[26] We collected fraction paraben

191   content information from various sources[1,12,37] and aggregated this data into a uniform

192   distribution (see SI Section S3 for details) with example values for shampoo and body lotion in

193   Table 1.

194   Up until this point, all calculations were described for a given product-chemical combination

195   used by the exposed population and do not account for the population with zero exposure. In

196   reality, different consumers use different combinations of products, with some products

197   containing paraben(s) and some not. Thus, in order to calculate aggregate exposure to PCPs, the

198   probability of occurrence of a given chemical within a PCP (percentage of products with a given

199   paraben) and the probability of product use (percentage of population that uses a given product)

200   need to be taken into account[1] (Figure S4, SI). The initial distributions created for the chemical

201   intake of the exposed population are thus adjusted for the unexposed population by adding the

202   appropriate amount of zeros representing non-exposure to the 44 distributions of 10^5 values

203   calculated for the exposed population.

204   *2.4 Product co-use*

205   To calculate the population exposure to parabens, the co-use of PCPs should also be taken

206   into account. For a given paraben there are eleven intake distributions representing each product

207 with several entries representing zero exposure based on the exposure probability; we randomly

208 permeated these distributions and then summed intake across products. This yields a single

209 aggregated intake distribution for each paraben (four distributions in total) with each entry

210 representing a random sum of product intake percentiles with some products having zero intakes.

211 We note that paraben exposure can occur via other media such as food and dust,[19,38,39] however

212 these media have been estimated to contribute substantially less to exposure levels when

213 compared to those occurring from direct PCP use.[1,12,39]

214   To demonstrate the potential usage of the PiF for risk screening, we also applied Eq. (2)

215 using the 99th percentiles for all values (except body weight, which was set to a constant 75 kg)

216 and added intake across all eleven products to yield a high-end usage scenario. This intake

217 estimate represents a user who uses all eleven products which all contain parabens, and does not

218 take into account any of the exposure adjustments described above. This intends to represent the

219 very high-end of potential exposure, within the intended use of PCPs.

220 *2.5 Converting external intake into urine concentrations*

221   The inclusion of the MC analysis to produce intake distributions also allows for comparison

222 to NHANES biomonitoring data which is in the form of population percentiles.[21] In order to

223 compare modeled intakes to biomonitoring data, we converted the dose taken in into urine

224 concentrations based on the urinary excretion fraction, f_{UE}, of the chemical. Following Angerer

225 et al.[40] the creatinine corrected chemical content in urine, C_{Cr} ($mg_{intake}\, mg_{excreted}^{-1}$), can be

226 estimated as

227 $$C_{Cr} = \frac{I \times BW \times f_{UE}}{Cr_{24h}} \tag{3}$$

228 where Cr_{24h} ($mg_{excreted}$ d^{-1}) is the daily creatinine excretion rate. There is very limited data on

229 f_{UE} for parabens available in the literature.[41] Thus, we estimated f_{UE} values based on measured

230 *in vitro* renal and hepatic clearance rates.[42,43] Uncertainty in f_{UE} was included in the analysis by

231 setting upper and lower bounds and running two sets of MC calculations using these high and

232 low bounds of f_{UE} (see SI, Section S5). We also added f_{UE} and Cr_{24h} from Eq. (3) to the Monte

233 Carlo analysis to account for population variability in these parameters. For further details on

234 f_{UE} see SI, Section S5. Eq. (3) was applied to each of the four paraben aggregate intake

235 distributions to yield distributions for paraben urinary concentrations. The percentiles from these

236 distributions can then be compared to the population based urinary concentration percentiles

237 available from NHANES (50th, 75th, 90th, and 95th percentiles for the years 2009-2010).[21]

238 **3. Results**

239 *3.1 Paraben Product Intake Fraction*

240 The median product intake fraction during the use-stage, PiF^{use} ranged from 2-88% (2.5^{th}-

241 97.5^{th} percentiles ranged from 0.1-99%) across the product-chemical combinations, with the

242 highest PiF^{use} for EtP in body lotion and the lowest for EtP in conditioner (Figure 1). This

243 indicates that a substantial fraction of the parabens in cosmetics penetrates the skin (Figure S2).

244 In contrast, the mean environmentally mediated PiF^{disp} was three to four orders of magnitude

245 lower than PiF^{use} for all product-chemical combinations, ranging from $10^{-4} – 10^{-3}$ % with the

246 highest PiF^{disp} for PrP in shampoo and the lowest for EtP in body lotion. This implies that the

247 focus can be on the use-stage exposure, which is substantially higher than environmentally

248 mediated exposure, such that the disposal-stage was subsequently excluded from the Monte

249 Carlo analysis. Within the use-stage, dermal aqueous uptake accounted for 78-99% of the total

250 PiF^{use} indicating that exposure to parabens in PCPs is dominated by direct dermal intake of

251 chemical applied to the skin (Figure S2). As the second main impact pathway, gaseous dermal

252 uptake accounted for 1 to 21% of PiF^{use} and inhalation represented only 0.1 to 1% of PiF^{use}.

253 Weschler and Nazaroff[44] also found that dermal gaseous uptake exceeds the inhalation pathway

254 for parabens.

255   The large range in PiF^{use} for parabens is mostly due to the variation in the application

256 duration of each PCP; PiF^{use} ranged from 6-50% for rinse-off products with a mean application

257 duration of 4 minutes, and from 50-80% for leave-on products with a mean application duration

258 of 14 hours. A plot of $PiF^{derm,aq}$ versus time (Figure S3a) for the mean product thickness, h (0.01

259 cm), shows that at 4 minutes (0.07 h), chemical uptake is still in the linear phase of the

260 exponential (with $PiF^{derm,aq}$ ranging from 0.2 – 0.4), whereas at 14 hours, uptake has reached its

261 plateau. For parabens this plateau occurs for $PiF^{derm,aq}$ at or above 80% at the mean product

262 thickness indicating that parabens are readily absorbed into the skin, which has been observed

263 empirically,[32,45] whereas this plateau may occur at a substantially lower $PiF^{derm,aq}$ for more

264 volatile chemicals. This observation is in-line with Gouin et al.[46] who suggested that wash-off

265 products (as opposed to leave-on products) are likely the dominant source of PCP chemicals to

266 WWTPs, noting that this depends on physicochemical properties. For a given chemical,

267 increasing product thickness can also reduce the fractional aqueous uptake (although not

268 necessarily the overall intake via this pathway); thus body wash (mean $h = 0.003$ cm) had a

269 larger $PiF^{derm,aq}$ than shampoo (mean $h = 0.03$ cm) (Figure 1) while both are rinse-off products

270 (this is demonstrated in a plot of $PiF^{derm,aq}$ versus time using the product thickness for body wash

271 and shampoo (Figure S3b)). Overall, mean product thicknesses ranged from 10^{-4} (body lotion) to

272 10^{-2} (shampoo) and are a function of the surface area of the application area and amount of

12

273 product applied (Table S1). The $PiF^{\text{derm,aq}}$ was more sensitive to product thickness for rinse-off

274 products as the uptake plateau is reached at 8 hours irrespective of leave-on product thickness

275 (Figure S3b).

276 *3.2 Population level paraben intakes*

277   Figure 2 presents the relationship between the potential doses of chemical used (assuming

278 100% product usage in the population and 100% paraben occurrence) and the effective chemical

279 intake after the indicated adjustment (i.e. product usage, paraben occurrence, and PiF) to the

280 previous adjustment. Adjusting for product usage reduced the potential dose by a factor of 1.4

281 for the four parabens on average, and the subsequent adjustment for paraben occurrence reduced

282 the potential dose by a factor 1.5 for MeP up to a factor 6 for BuP. Multiplying the effectively

283 applied dose (i.e. after adjusting for product usage and occurrence) by the PiF reduced the

284 population exposure by 3, 1.5, 4, and 2 times for MeP, EtP, PrP, and BuP, respectively. Overall,

285 the final adjusted intakes were 7, 11, 13 and 20 times lower than the potential dose for MeP, EtP,

286 PrP, and BuP, respectively. Cowan-Ellsberry and Robison[1] also found that applying these

287 refinements substantially reduced the population exposure of parabens in PCPs with reductions

288 ranging from a factor 2 to 12.5. Using PrP as an example, body wash, shampoo, body lotion, and

289 conditioner contributed most to the potential applied dose (26, 22, 18, and18%). Once the

290 refinements were applied, body lotion and body wash dominated the total intake (38% and 28%,

291 respectively), whereas shampoo and conditioner combined made up only 13% of the total intake

292 due to lower exposure duration and PiF (Figure 2).

293   Accounting for product co-use yielded the final modeled exposure distributions for the four

294 parabens (Figure 3). Based on these distributions ~100, 75, 97, and 69% of the adult female

295 population is exposed (i.e. with non-zero intakes) to MeP, EtP, PrP, and BuP, respectively which

296 compares well to 99, 42, 93, and 47% detection reported for all urine samples (i.e. representing

297 the entire population) from NHANES[22] (Figure S5, SI). The higher detection frequency we

298 determined for female adults are consistent with the highest NHANES paraben urine

299 concentrations for female adults compared to other population groups. MeP and PrP had the

300 highest probability of exposure out of the four parabens (Figure 3), due to their higher frequency

301 of occurrence, while the modeled EtP and BuP intakes were strongly reduced when considering

302 occurrence (Figure 3).

303   The mean (2.5th-97.5th percentile) modeled population intakes were 0.2 (3×10^{-3}-0.8), 0.03 (0-

304 0.2), 0.06 (0-0.3), 0.02 (0-0.1) mg kg^{-1} d^{-1} for MeP, EtP, PrP, and BuP, respectively (Table 2).

305 These modeled mean intakes fall in-between those found by Cowan-Ellsberry and Robison[1] and

306 Guo and Kannan[12] for paraben exposure due to PCPs (Table S9), noting that these studies did not

307 take population variability into account.

308   Since some consumers may indeed use all PCP types which may all contain a given paraben,

309 we calculated a high-end intake without applying the exposure adjustments for population

310 exposure (i.e. we did not adjust for product usage, paraben occurrence, and co-use), yielding

311 doses of 8, 3, 4, and 2 mg kg^{-1} d^{-1} for MeP, EtP, PrP, and BuP respectively and are approximately

312 an order of magnitude larger than the 99th percentile stochastically based adjusted exposure

313 estimates. While these high-end estimates of exposures may not necessarily be likely, they may

314 be possible and provide upper end conservative exposure estimates.

315 *3.3 Conversion to biomonitoring levels and comparison to NHANES*

316 Combining urinary excretion rates with the modeled intakes (with all adjustments, i.e. product

317 usage, paraben occurrence, and *PiF*^{tot}) allows for conversion to urinary concentration

318 distributions, which can be directly compared to the 50th, 75th, 90th, and 95th percentiles of the

319   NHANES biomonitoring data. Modeled urine concentration percentiles reflect well the

320   NHANES variation of three orders of magnitude across parabens and percentiles and were well

321   correlated ($R^2 = 0.9$ comparing the log). Modeled values were within a factor of three (except for

322   one value) using the *in vitro* estimated values of f_{UE}. When taking uncertainty into account, all

323   modeled values were in agreement with NHANES values (Figure 4). As discussed above, the

324   effect of applying the PiF^{tot} reduced the product usage and paraben occurrence adjusted intakes

325   on average by a factor of 1.5 to 4 (Figure 2) which is a reflection of the median PiF^{tot} being

326   larger than 50% for the majority of the products (i.e the leave-on products). This indicates that

327   the three orders of magnitude variation in the biomonitoring data is not only a function of the PiF

328   but also population variability and the other included exposure adjustments. The comparison to

329   biomonitoring data suggests that the estimated PiFs for parabens are within an order of

330   magnitude of actual intake fractions.

331   **4. Discussion**

332   The PiF is a useful metric to compare product specific chemical intake due to various

333   near- and far-field exposure pathways and routes due to PCP use, and for differentiating

334   exposure between leave-on and rinse-off products instead of assuming a fixed fraction of

335   chemical absorbed into the skin, which may lead to overestimates of the exposure. For parabens,

336   model results suggested that dermal aqueous and gaseous uptake were the dominant exposure

337   pathways and the inhalation and far-field pathways were substantially lower in comparison.

338   Gouin et al. (2013) suggested that the use-phase of PCPs may be used to estimate down-the-drain

339   emissions of PCP chemicals and the framework presented here can also be applied in this

340   context. Furthermore, the PiF for PCPs has an analytical solution and can be calculated based on

341   physicochemical properties and product usage characteristics and thus lends itself to rapid

342   computational exposure estimates. While this study applied stochastic techniques in-line with

343   Tier 2 exposure calculations[18] to facilitate comparison with bioactivity data, the PiF modeling

344   framework for PCPs can also be readily applied in Tier 1 screening assessments as recommended

345   by Shin et al.[6]

346   Other exposure media for parabens include food and dust[19,38,39], however these sources

347   have been previously found substantially lower than PCPs.[1,12,39] Soni et al.[19] estimated that the

348   highest likely food intake for MeP and PrP is 0.01 mg kg^{-1} d^{-1} (1 mg d^{-1} normalized to 75 kg used

349   in this study), which is 20 and 6 times lower than our modeled mean intake due to PCP usage for

350   MeP and PrP, respectively. The 95th percentile food intake for the four parabens ranged from 10^{-4}-10^{-6} mg kg^{-1} d^{-1} based on measured food concentrations of parabens in U.S.[39] Intake of the four

352   parabens via dust based on measured dust concentrations was estimated to range between 10^{-6}-10^{-9} mg kg^{-1} d^{-1} [38] and is several orders of magnitude lower than modeled PCP intakes.

354   To predict paraben intake accurately, it is crucial to account for product usage, paraben

355   occurrence within products, and population variability. Accounting for these exposure

356   adjustments and using modeled PiF for parabens in PCPs yielded agreement between modeled

357   and NHANES urine concentrations. This indicates that a detailed exposure calculation taking

358   into account the chemical and product dependent PiF, exposure probability, and population

359   variability can be an effective method to predict population level chemical intake associated with

360   PCPs.

361   Uncertainty on the fraction urinary excretion, f_{UE}, is considerable when converting

362   chemical intakes and the limited empirical data available in the literature for parabens resulted in

363   high uncertainty in estimated urine concentrations. Physicochemical property based estimates of

364   pharmacokinetic parameters have recently been made available[42,47] and may be useful for

365   comparing exposure with high-throughput toxicity data for a larger number of chemicals. While

366   the mean modeled urine levels overestimate those of NHANES the R^2 of 0.87 for the log fit of

367   modeled versus measured indicates that the modeling approach presented here was able to

368   capture the exposure patterns of the four parabens well.

369   An additional challenge when estimating aggregate exposure is to effectively take into

370   account product co-use.[1] While several PCP usage studies report some data on product co-use,

371   this information cannot be practically applied to a comprehensive PCP study as the data

372   presentation is often incomplete; for example, only the most commonly used combinations, the

373   correlation between the use of two products (rather than multiple products), or data on different

374   sets of PCPs are presented,[1,48,49] and certain PCPs of interest are not included in that dataset. By

375   accounting for the probability of using a product, we were able to provide an initial reasonable

376   estimate of product co-use, which could be complemented by multiple product usage conditional

377   probabilities. Furthermore, co-use becomes even more complex when chemicals occur in

378   different product types, for example PCPs and cleaning products and alternative methods for

379   taking co-use into account may be needed.

380   Within the context of risk screening, the exposure refinements needed for a population

381   level calculation may not necessarily be needed to calculate exposure for high-end product users

382   (for example, those who use several PCPs with high-end product masses within the intended

383   product usage) to protect all users rather than an average user. For example, exposure estimates

384   can be compared with the allowable daily intake (ADI) to inform risk of parabens in PCPs.

385   While there is no ADI for EtP and BuP, the combined ADI for MeP and PrP in the European

386   Union is 0-10 mg kg^{-1} d^{-1} [19,23] which is within an order of magnitude of both the high-end user

387   combined intake of 12 mg kg^{-1} d^{-1} and the 99th percentile stochastically estimated intake (with

388   exposure adjustments) of 1.5 mg kg^{-1} d^{-1}.

389   We presented a detailed population level PCP exposure model which is able to predict the

390   three orders of magnitude of variation in NHANES paraben urine concentrations. The PCP

391   product intake fraction model can be readily incorporated into rapid exposure models and can be

392   combined with concentration databases such as the recently released Consumer Product

393   Chemical Profile database CPCPdb[26] to estimate chemical intakes due to PCP use.

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References

407   1   Cowan-Ellsberry CE, Robison SH. Refining aggregate exposure: example using parabens.
408   *Regul Toxicol Pharmacol* 2009; **55**: 321–9.

409   2   Gosens I, Delmaar CJE, Ter Burg W, de Heer C, Schuur AG. Aggregate exposure
410   approaches for parabens in personal care products: a case assessment for children between
411   0 and 3 years old. *J Expo Sci Environ Epidemiol* 2014; **24**: 208–14.

412   3   Wambaugh JF, Setzer RW, Reif DM, Gangwal S, Mitchell-Blackwood J, Arnot JA *et al.*
413   High-throughput models for exposure-based chemical prioritization in the ExpoCast
414   project. *Environ Sci Technol* 2013; **47**: 8479–88.

415   4   Isaacs KK, Glen WG, Egeghy P, Goldsmith M-R, Smith L, Vallero D *et al.* SHEDS-HT:
416   An Integrated Probabilistic Exposure Model for Prioritizing Exposures to Chemicals with
417   Near-Field and Dietary Sources. *Environ Sci Technol* 2014; **48**: 12750–9.

418   5   Wetmore BA, Wambaugh JF, Ferguson SS, Sochaski MA, Rotroff DM, Freeman K *et al.*
419   Integration of dosimetry, exposure, and high-throughput screening data in chemical
420   toxicity assessment. *Toxicol Sci* 2012; **125**: 157–74.

421   6   Shin H-M, Ernstoff A, Arnot JA, Wetmore BA, Csiszar SA, Fantke P *et al.* Risk-Based
422   High-Throughput Chemical Screening and Prioritization using Exposure Models and in
423   Vitro Bioactivity Assays. *Environ Sci Technol* 2015; **49**: 6760–6771.

424   7   Shin H-M, McKone TE, Bennett DH. Intake fraction for the indoor environment: a tool
425   for prioritizing indoor chemical sources. *Environ Sci Technol* 2012; **46**: 10063–72.

426   8   Braun JM, Just AC, Williams PL, Smith KW, Calafat AM, Hauser R. Personal care
427   product use and urinary phthalate metabolite and paraben concentrations during pregnancy
428   among women from a fertility clinic. *J Expo Sci Environ Epidemiol*; **24**: 459–66.

429   9   Parlett LE, Calafat AM, Swan SH. Women's exposure to phthalates in relation to use of
430   personal care products. *J Expo Sci Environ Epidemiol* 2013; **23**: 197–206.

431   10   Wormuth M, Demou E, Scheringer M, Hungerbühler K. Assessments of Direct Human
432   Exposure—The Approach of EU Risk Assessments Compared to Scenario Based Risk
433   Assessment. *Risk Anal* 2007; **27**: 979–990.

434   11   Jolliet O, Fantke P. Human Toxicity. In: Hauschild MZ, Huijbregts MAJ (eds). *Life Cycle*
435   *Impact Assessment*. Springer Press: Dordrecht, 2015, pp 75–96.

436   12   Guo Y, Kannan K. A Survey of Phthalates and Parabens in Personal Care Products from
437   the United States and Its Implications for Human Exposure. *Environ Sci Technol* 2013;
438   **47**: 14442–14449.

19

439 13   Ten Berge W. A simple dermal absorption model: Derivation and application.
440   *Chemosphere* 2009; **75**: 1440–1445.

441 14   Wilschut A, ten Berge WF, Robinson PJ, McKone TE. Estimating skin permeation. The
442   validation of five mathematical skin permeation models. *Chemosphere* 1995; **30**: 1275–
443   1296.

444 15   Delmaar C, Bokkers B, Ter Burg W, Schuur G. Validation of an aggregate exposure
445   model for substances in consumer products: a case study of diethyl phthalate in personal
446   care products. *J Expo Sci Environ Epidemiol* 2014. doi:10.1038/jes.2014.68.

447 16   Tibaldi R, ten Berge W, Drolet D. Dermal absorption of chemicals: estimation by IH
448   SkinPerm. *J Occup Environ Hyg* 2014; **11**: 19–31.

449 17   Jolliet O, Ernstoff AS, Csiszar SA, Fantke P. Defining Product Intake Fraction to Quantify
450   and Compare Exposure to Consumer Products. *Environ Sci Technol* 2015; **49**: 8924–31.

451 18   Embry MR, Bachman AN, Bell DR, Boobis AR, Cohen SM, Dellarco M *et al.* Risk
452   assessment in the 21st century: roadmap and matrix. *Crit Rev Toxicol* 2014; **44 Suppl 3**:
453   6–16.

454 19   Soni MG, Carabin IG, Burdock GA. Safety assessment of esters of p-hydroxybenzoic acid
455   (parabens). *Food Chem Toxicol* 2005; **43**: 985–1015.

456 20   Ye X, Bishop AM, Reidy JA, Needham LL, Calafat AM. Parabens as Urinary Biomarkers
457   of Exposure in Humans. *Environ Health Perspect* 2006; **114**: 1843–1846.

458 21   CDC. Centers for Disease Control and Prevention. Fourth National Report on Human
459   Exposure to Environmental Chemicals: Updated Tables. US Department of Health and
460   Human Services. 2014.http://www.cdc.gov/exposurereport/.

461 22   Calafat AM, Ye X, Wong L-Y, Bishop AM, Needham LL. Urinary concentrations of four
462   parabens in the U.S. population: NHANES 2005-2006. *Environ Health Perspect* 2010;
463   **118**: 679–85.

464 23   Boberg J, Taxvig C, Christiansen S, Hass U. Possible endocrine disrupting effects of
465   parabens and their metabolites. *Reprod Toxicol* 2010; **30**: 301–12.

466 24   Błędzka D, Gromadzińska J, Wąsowicz W. Parabens. From environmental studies to
467   human health. *Environ Int* 2014; **67**: 27–42.

468 25   Rosenbaum R, Huijbregts M, Henderson A, Margni M, McKone T, van de Meent D *et al.*
469   USEtox human exposure and toxicity factors for comparative assessment of toxic
470   emissions in life cycle analysis: sensitivity to key chemical properties. *Int J Life Cycle*
471   *Assess* 2011; **16**: 710–727.

472 26 Goldsmith M-R, Grulke CM, Brooks RD, Transue TR, Tan YM, Frame a *et al.*
473   Development of a consumer product ingredient database for chemical exposure screening
474   and prioritization. *Food Chem Toxicol* 2014; **65**: 269–79.

475 27 Bremmer HJ, Prud'homme de Lodder L, van Engelen J. Cosmetics Fact Sheet. To assess
476   the risks for the consumer. Updated version for ConsExpo 4. RIVM report
477   320104001/2006. National Institute for Public Health and the Environment, Bilthoven,
478   The Netherlands, 2006.

479 28 Caon T, Costa ACO, de Oliveira MAL, Micke GA, Simões CMO. Evaluation of the
480   transdermal permeation of different paraben combinations through a pig ear skin model.
481   *Int J Pharm* 2010; **391**: 1–6.

482 29 Kitagawa S, Li H, Sato S. Skin permeation of parabens in excised guinea pig dorsal skin,
483   its modification by penetration enhancers and their relationship with n-octanol/water
484   partition coefficients. *Chem Pharm Bull (Tokyo)* 1997; **45**: 1354–7.

485 30 Nanayakkara GR, Bartlett A, Forbes B, Marriott C, Whitfield PJ, Brown MB. The effect
486   of unsaturated fatty acids in benzyl alcohol on the percutaneous permeation of three model
487   penetrants. *Int J Pharm* 2005; **301**: 129–39.

488 31 Nicoli S, Zani F, Bilzi S, Bettini R, Santi P. Association of nicotinamide with parabens:
489   effect on solubility, partition and transdermal permeation. *Eur J Pharm Biopharm* 2008;
490   **69**: 613–21.

491 32 Dal Pozzo A, Pastori N. Percutaneous absorption of parabens from cosmetic formulations.
492   *Int J Cosmet Sci* 1996; **18**: 57–66.

493 33 Sugibayashi K, Todo H, Oshizaka T, Owada Y. Mathematical model to predict skin
494   concentration of drugs: toward utilization of silicone membrane to predict skin
495   concentration of drugs as an animal testing alternative. *Pharm Res* 2010; **27**: 134–42.

496 34 Loretz LJ, Api AM, Barraj LM, Burdick J, Dressler WE, Gettings SD *et al.* Exposure data
497   for cosmetic products: lipstick, body lotion, and face cream. *Food Chem Toxicol* 2005; **43**:
498   279–291.

499 35 Loretz L, Api AM, Barraj L, Burdick J, Davis DA, Dressler W *et al.* Exposure data for
500   personal care products: Hairspray, spray perfume, liquid foundation, shampoo, body wash,
501   and solid antiperspirant. *Food Chem Toxicol* 2006; **44**: 2008–2018.

502 36 Loretz LJ, Api AM, Babcock L, Barraj LM, Burdick J, Cater KC *et al.* Exposure data for
503   cosmetic products: facial cleanser, hair conditioner, and eye shadow. *Food Chem Toxicol*
504   2008; **46**: 1516–24.

505 37 Rastogi SC, Schouten A, de Kruijf N, Weijland JW. Contents of methyl-, ethyl-, propyl-,
506   butyl- and benzylparaben in cosmetic products. *Contact Dermatitis* 1995; **32**: 28–30.

507 38 Wang L, Liao C, Liu F, Wu Q, Guo Y, Moon H-B *et al.* Occurrence and Human Exposure
508   of p-Hydroxybenzoic Acid Esters (Parabens), Bisphenol A Diglycidyl Ether (BADGE),
509   and Their Hydrolysis Products in Indoor Dust from the United States and Three East
510   Asian Countries. *Environ Sci Technol* 2012; **46**: 11584–11593.

511 39 Liao C, Liu F, Kannan K. Occurrence of and dietary exposure to parabens in foodstuffs
512   from the United States. *Environ Sci Technol* 2013; **47**: 3918–25.

513 40 Angerer J, Aylward LL, Hays SM, Heinzow B, Wilhelm M. Human biomonitoring
514   assessment values: approaches and data requirements. *Int J Hyg Environ Health* 2011;
515   **214**: 348–60.

516 41 Søeborg T, Frederiksen H, Andersson A-M. Considerations for estimating daily intake
517   values of nonpersistent environmental endocrine disruptors based on urinary
518   biomonitoring data. *Reproduction* 2014; **147**: 455–63.

519 42 Kirman CR, Aylward LL, Wetmore BA, Thomas RS, Sochaski M, Ferguson SS *et al.*
520   Quantitative Property–Property Relationship for Screening-Level Prediction of Intrinsic
521   Clearance: A Tool for Exposure Modeling for High-Throughput Toxicity Screening Data.
522   *Appl Vitr Toxicol* 2015; **1**: 140–146.

523 43 Wetmore BA, Wambaugh JF, Allen B, Ferguson SS, Sochaski MA, Setzer RW *et al.*
524   Incorporating High-Throughput Exposure Predictions with Dosimetry-Adjusted In Vitro
525   Bioactivity to Inform Chemical Toxicity Testing. *Toxicol Sci* 2015.
526   doi:10.1093/toxsci/kfv171.

527 44 Weschler CJ, Nazaroff WW. Dermal uptake of organic vapors commonly found in indoor
528   air. *Environ Sci Technol* 2014; **48**: 1230–7.

529 45 El Hussein S, Muret P, Berard M, Makki S, Humbert P. Assessment of principal parabens
530   used in cosmetics after their passage through human epidermis-dermis layers (ex-vivo
531   study). *Exp Dermatol* 2007; **16**: 830–6.

532 46 Gouin T, van Egmond R, Sparham C, Hastie C, Chowdhury N. Simulated use and wash-
533   off release of decamethylcyclopentasiloxane used in anti-perspirants. *Chemosphere* 2013;
534   **93**: 726–34.

535 47 Arnot JA, Brown TN, Wania F. Estimating screening-level organic chemical half-lives in
536   humans. *Environ Sci Technol* 2014; **48**: 723–30.

537 48 Biesterbos JWH, Dudzina T, Delmaar CJE, Bakker MI, Russel FGM, von Goetz N *et al.*
538   Usage patterns of personal care products: important factors for exposure assessment. *Food
539   Chem Toxicol* 2013; **55**: 8–17.

540   49   Manová E, von Goetz N, Keller C, Siegrist M, Hungerbühler K. Use patterns of leave-on
541   personal care products among Swiss-German children, adolescents, and adults. *Int J*
542   *Environ Res Public Health* 2013; **10**: 2778–98.

543   50   US EPA. Estimation Programs Interface Suite^TM for Microsoft® Windows, v 4.11. 2012.

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Tables

|	MeP	EtP	PrP	BuP	Notes and Reference
$logK_{aw}$	-5.6	-6.0	-5.2	-4.9	Calculated from solubility and vapor pressure, EPI Suite [50]. Values listed here are at 25 ºC and were corrected to skin temperature of 32 ºC for use in the model (see Sec. S.1).
K_p^{aq} (cm h^{-1}) (geometric mean, GSD^2)	0.012, 31	0.009, 19	0.009, 31	0.023, 31	Lognormal distribution. See Table S3[a]
K_p^{gas} (cm h^{-1}) (geometric mean, GSD^2)	4200, 28	10000, 28	1400, 28	1800, 28	Lognormal distribution. Geometric mean calculated using equation in Table S1. GSD^2 was set to the mean of K_p^{aq} GSD^2. Values are at 25ºC and were corrected to skin temperature.
f_p shampoo (%) (low – high)	0.01 to 0.2	0 to 2×10^{-4}	1×10^{-3} to 0.2	2×10^{-4} to 0.045	Uniform distribution. See Table S4[b]
f_p body lotion (%) (low – high)	0.01 to 0.29	0.01 to 0.2	0.01 to 0.2	0 to 0.085	Uniform distribution. See Table S4[b]
f_p range for all products % (low – high)	8×10^{-6} to 0.5	0 to 0.35	0 to 0.28	0 to 0.27	Uniform distribution. See Table S4[b]
M_p shampoo (g d^{-1}) (2.5th -97.5th percentile)	1.7 to 34				Gamma distribution. [35]
M_p body lotion (g d^{-1}) (2.5th -97.5th percentile)	2.5 to 21				Gamma distribution. [34]
M_p range for all products (g d^{-1})	8×10^{-4} to 44 (Min 2.5th – max 97.5th percentile)				[34–36]. See Figure S1

548 **Table 1:** Summary input data for main model parameters for methyl, ethyl, propyl, and butyl
549 paraben. Further information and input data can be found in the SI. Notes: [a]See Table S3 for
550 references. [b]Based on data from [1,12,37]. GSD^2 = geometric standard deviation squared.

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554 **Figures**
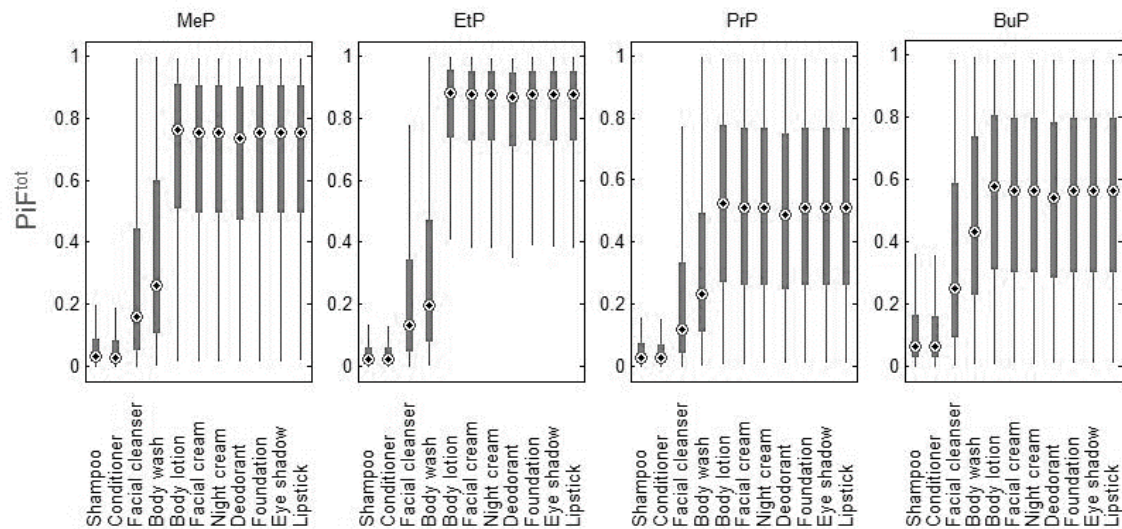
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556 **Figure 1:** Modeled total product intake fraction (PiF^{tot}) for the 11 personal care products for
557 MeP, EtP, PrP, and BuP (from left to right). The circles represent the median, the solid boxes
558 represent the 25th and 75th percentiles, and the lines represent the 2.5^{th} and 97.5^{th} percentiles of
559 PiF^{tot} calculated using Monte Carlo simulation.

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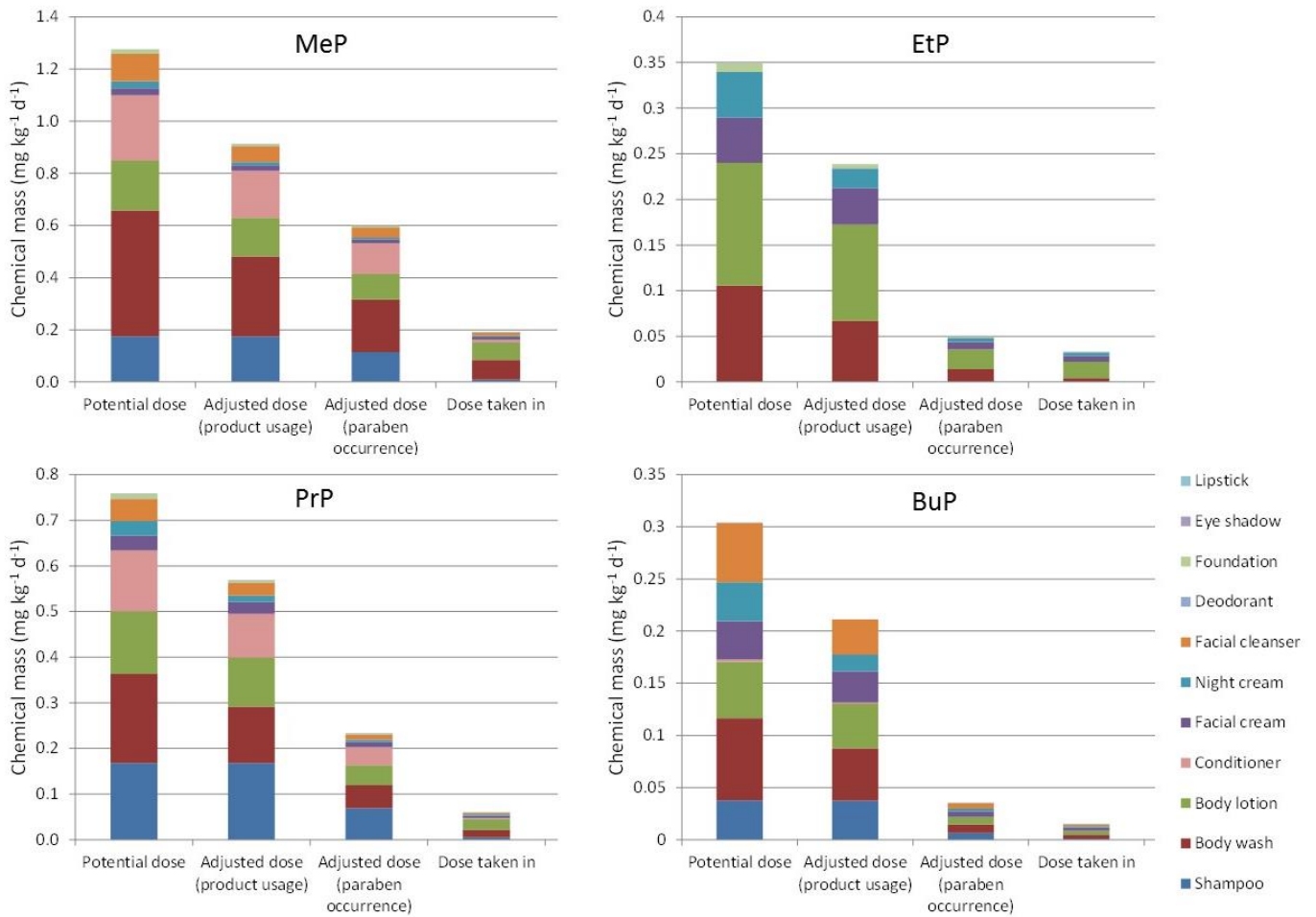
Figure 2: Reduction in potential applied chemical dose due to population PCP usage, paraben occurrence in products, and product intake fraction to yield the mean dose taken in for each product-chemical combination calculated by Monte Carlo simulations. The reductions were applied sequentially, thus the last column represents the dose based on all three reductions.

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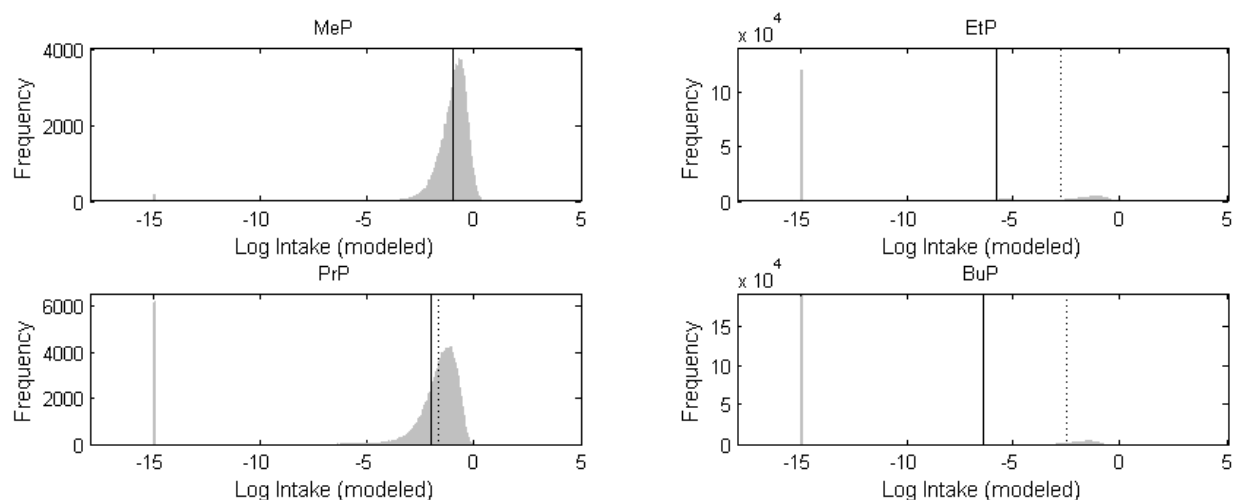
Figure 3: Modeled log intake (mg kg d^{-1}) distributions for the four parabens taking into account probability of exposure and product co-use. The grey solid vertical lines indicate the population with zero exposure (zero intakes were adjusted to a nominally low value (1×10^{-15}) to make them visible on a log scale). The dashed line indicates the geometric mean of the exposed population and the black solid line indicates the geometric mean of the entire population (with adjusted zero intakes).

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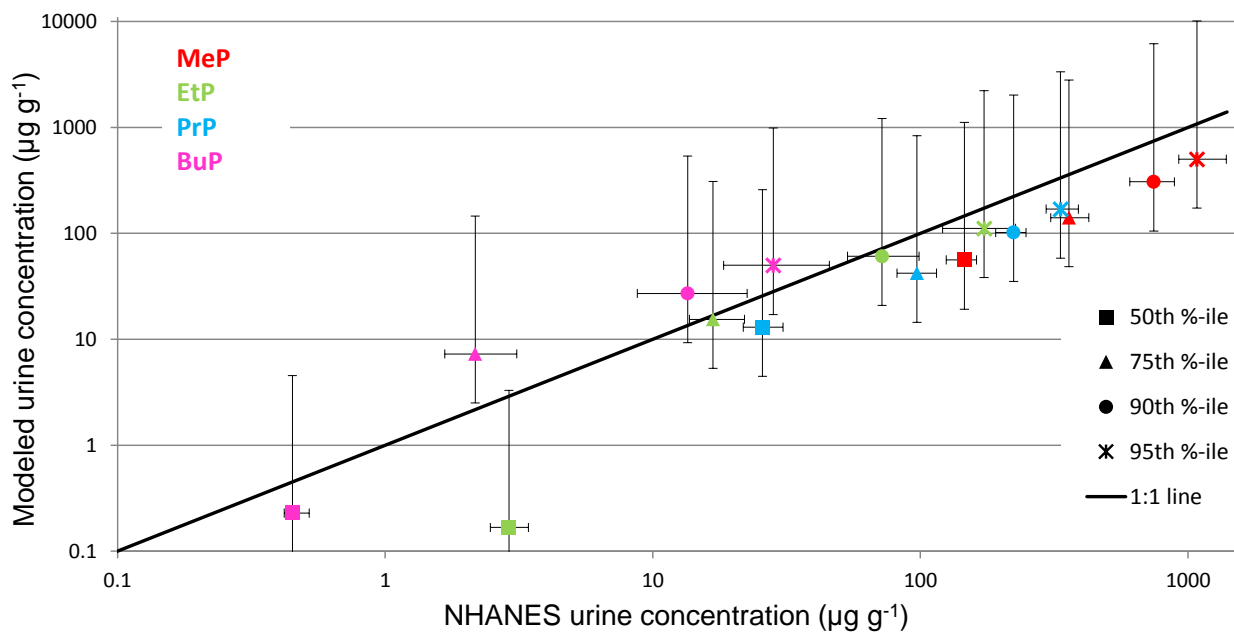
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584 **Figure 4:** Modeled urine concentrations from the Monte Carlo calculations versus NHANES
585 urine concentrations. Vertical error bars on the modeled values represent uncertainty in fraction
586 urinary excretion and horizontal error bars on the NHANES values represent the 95th confidence
587 interval on each percentile. The solid line indicates perfect agreement between modeled and
588 measured values (1:1 line).
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