重点：（第三阶段：全局参数的敏感性分析、输出不确定性）

Local sensitivity analysis commonly does not investigate the impact of parameters correlations on model outputs since it generally does not consider parameters having a specific distribution. Global sensitivity analysis (GSA) which samples all parameters over their specific distributions, however, can evaluate simultaneously the relative contributions of all model parameters and their potential interactions to a set of specified model outputs variance (Li et al., 2010). Therefore, GSA was conducted with the “soboljansen” package of R language used for assessing the model parameters importance while considering their uncertainty and correlations in this study. Maximum concentration (Cmax) and 24-h area under the curve (AUC) of unconjugated BPS in human blood were considered as model outputs.

Monte Carlo (MC) simulation was used to assess the uncertainty on the model output. In the MC analysis, values are randomly sampled from probability distributions defined for variables of interest. As for FTP and Fabsorb measured in this study, truncated normal distribution was used to account for uncertainty in a physiologically plausible way (95 % of the distributions equals measured mean ± 1.96 times standard deviation (SD)). As for Fabsorb of BPA for PCPs exposure pathway and chemical-specific parameters for dermal absorption, we randomly varied the parameters using truncated normal distributions. Among them, the mean values were derived from parametrization of our adapted models and coefficients of variation (CV = SD / mean) were used to describe the relative extent of variability at the value of 30 %

Other model parameters, including physiological (Table S5) and chemical-specific parameters (Tables S6–S9), were randomly sampled under either truncated normal distribution or trapezoidal distribution adopted from Karrer et al. (2018). We conducted the uncertainty analysis for serum concentrations of BPs in women of childbearing age (18 to 45 years). 4 μg/kg bw/day was used via both the dermal exposure pathways as model inputs for all BPs (EFSA, 2015). We simulated dermal exposure by touching TP and using PCPs twice a day, in the morning and in the evening corresponding with Karrer et al. (2018, 2019). The simulation was run for 4 d to achieve a steady-state concentration in serum. Each MC simulation included 10,000 iterations. Uncertainty coefficients which equal the ratio of 95th percentile (P95) and median (P50) of the model outputs were used for evaluating model uncertainty and the values greater than or equal to 2, between 0.3 and 2 and less than or equal to 0.3 correspond to high, medium and low uncertainty, respectively (WHO, 2010).

此段翻译：

局部敏感性分析通常不研究参数相关性对模型输出的影响，因为它通常不考虑具有特定分布的参数。 然而，全局敏感性分析（GSA）对特定分布上的所有参数进行采样，可以同时评估所有模型参数的相对贡献及其对一组指定模型输出方差的潜在相互作用（Li et al., 2010）。 因此，本研究中使用R语言的“soboljansen”包进行GSA，用于评估模型参数的重要性，同时考虑它们的不确定性和相关性。 人血液中未结合的 BPS 的最大浓度 (Cmax) 和 24 小时曲线下面积 (AUC) 被视为模型输出。

蒙特卡罗（MC）模拟用于评估模型输出的不确定性。 在 MC 分析中，值是从为感兴趣的变量定义的概率分布中随机采样的。 对于本研究中测量的 FTP 和 Fabsorb，使用截断正态分布以生理上合理的方式解释不确定性（95% 的分布等于测量平均值 ± 1.96 倍标准差 (SD)）。 至于用于 PCP 暴露途径的 BPA 的 Fabsorb 和用于真皮吸收的化学特异性参数，我们使用截断正态分布随机改变参数。 其中，平均值来自我们适应模型的参数化，变异系数（CV = SD /平均值）用于描述30%值时的相对变异程度

其他模型参数，包括生理参数（表 S5）和化学特定参数（表 S6-S9），是在 Karrer 等人采用的截断正态分布或梯形分布下随机采样的。 （2018）。 我们对育龄妇女（18 至 45 岁）血清 BP 浓度进行了不确定性分析。 通过两种皮肤暴露途径使用 4 μg/kg bw/天作为所有 BP 的模型输入（EFSA，2015）。 我们通过触摸 TP 并每天使用 PCP 两次（早上和晚上）来模拟皮肤暴露，与 Karrer 等人的研究相对应。 （2018、2019）。 模拟运行 4 天以达到血清中的稳态浓度。 每个 MC 模拟包括 10,000 次迭代。 不确定性系数等于模型输出的第95个百分位数（P95）与中位数（P50）的比率用于评估模型不确定性，大于或等于2、0.3和2之间以及小于或等于0.3的值对应于 分别为高、中和低不确定性（WHO，2010）。

The adapted models were utilized to predict the toxicokinetic process of four BPs when adult women (18 to 45 years) are exposed to them via TPs and/or PCPs routes. The concentrations of unconjugated BPs in gonads of female adults were applied to outcome metrics since the gonads are susceptible to the effects of exposure to endocrine disrupting chemicals (Karrer et al., 2018). The dermal exposure scenario used for uncertainty analysis was also applied for the evaluation. PBPK models were run for 4 days to yield the stable concentration–time curve of individual BPs in gonads. The predictions of the adapted dermal PBPK models were also compared with those of the previous ones (Karrer et al., 2018).