Table 1: Chemical-specific parameters used in the steady-state algorithm.

Parameter	Chemical	
	Benzene[(a)]	1,4-Dioxane[(b)]
$V\max_c$ (mg/h-kg$^{0.75}$)	2.11	0.27
Km (mg/L)	0.1	3.0
Blood : air partition coefficient (P_b)	7.4	3650
Exposure concentration (mg/m^3, UF × RfC)[(c)]	0.3	3

[(a)][22]. [(b)][23]. [(c)][10].

BW: body weight; Km: Michaëlis-Menten constant, P_b: blood : air partition coefficient, RfC: reference concentration; UF: interindividual uncertainty factor; $V\max_c$: constant maximum rate of metabolism.

value of a parameter (i.e., 95th) and its central tendency value (i.e., median) in the whole population or between an upper percentile value in a presumed susceptible subpopulation and the central tendency value in the general healthy population [8, 9].

Neither the historical definitions of IVF [4] nor the IPCS guidance document on CSAFs [8] clearly defines the "average healthy individual," forming the point of comparison for the presumed sensitive subpopulations. Particularly, it is unclear as to whether this individual is the average healthy adult or the average healthy individual from the whole population (which includes both healthy adults and sensitive subpopulations). But presumably because the POD used to derive the RfD or RfC is generally determined in healthy adults (animal or human) [10], HKAF evaluations conducted using experimental data for drugs [11–13] or PBPK model simulation data for environmental toxicants [14–16] have relied on what can be called a "distinct subpopulation" approach. Thus, the experimental or simulated data in the presumed susceptible individuals (e.g., neonates, pregnant women, elderly, polymorphic individuals) have often been compared with the corresponding data in healthy adults.

Alternatively, HKAF can be quantified using a "whole population" approach as done recently by Mörk and Johanson [17]. In this study, HKAFs were calculated for inhaled acetone based on a simulated distribution of steady-state blood concentration in an entire population, including adults and various age-defined groups of children. The PBPK modeling results in the different subgroups were weighted according to demographic representation in Sweden. Excluding the endogenous production of acetone, an HKAF of 1.9 was obtained by dividing the 95th percentile value of the entire population by the median. In comparison, using the 95th percentile value of that same dose metric in 3-month-old babies as well as 10 and 15 yr old children resulted in HKAFs of 2, 2.4, and 1.7, respectively.

The hypothesis that the HKAF determined upon the "whole population" approach is quite different from the one determined based on the "distinct subpopulation" approach stems from the results of Mörk and Johanson [17]. This potential difference could be significant from a regulatory standpoint because it may not lead to comparable levels of protection for the different subgroups that compose the whole population. It is also not known whether the population composition and the chemical considered may impact this potential difference. Thus, the objective of the current study was to evaluate the magnitude and adequacy of the HKAFs determined by the "whole population" approach as compared to the "distinct subpopulation" approach. In effect, population distributions of internal dose metrics following chronic exposure to two chemicals exhibiting different clearance characteristics were used to compute the HKAF as

(i) the ratio of the upper percentile value in the entire population including adults and nonadults over the median in adults and in this entire population;

(ii) the ratio of the upper percentile value in presumed susceptible subpopulation over the median in adults and in the entire population including adults and non-adults.

2. Methods

A physiologically based steady-state algorithm combined with Monte Carlo simulation software was used to generate population distributions of blood concentration (CAss) and rate of metabolism (RAM) for chronic inhalation exposure to two chemicals with contrasting systemic clearance characteristics. The population distributions were reconstructed based on different proportions of randomly selected adults, elderly, children, neonates, and PW, and they were used to compute HKAFs based on "whole population" and "distinct subpopulation" approaches.

2.1. Selection of Surrogate Chemicals and Their Specific Parameters. Two VOCs were chosen as surrogate chemicals because they exhibit contrasting systemic clearances based on their pulmonary clearance potential (different blood : air partition coefficient (P_b)) and their hepatic clearance (different hepatic extraction ratios). Benzene was chosen as an extensively cleared chemical because of its high pulmonary clearance (low P_b, 7.4) and high hepatic extraction ratio. Conversely, 1,4-dioxane was chosen as a poorly cleared chemical due to its low pulmonary clearance (P_b = 3650) and low hepatic extraction ratio. While benzene is a known substrate of CYP2E1 [18], for which extensive data on interindividual variability are available [19, 20], 1,4-dioxane was included in this study to facilitate the coverage of a range of physico/biochemical properties of potential substrates of CYP2E1 [21]. Chemical-specific parameters are indicated in Table 1 and were taken from the literature [10, 22, 23]. The choice of these two surrogate VOCs and associated kinetic parameters was undertaken to reflect the range of kinetic characteristics of hypothetical substances for evaluating the HKAF. As such, the present modeling study did not focus on any aspect of the risk assessment relating to these specific chemicals.

2.2. Use of a Biologically Based Steady-State Model for the Simulation of Continuous Inhalation Exposure in Different Subpopulations. The current study relies on the use of