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UNCERTAINTY ANALYSIS OF DIOXIN-LIKE POLYCHLORINATED BIPHENYLS–RELATED TOXIC EQUIVALENTS IN FISH

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Abstract—The toxic equivalent (TEQ) concept is widely used to assess toxicity potential of a dioxin-like chemical mixture. The TEQ approach converts concentrations of various dioxin-like compounds into a single concentration that is toxicologically equivalent to the most toxic dioxin compound, 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (2,3,7,8-TCDD), using toxic equivalency factors (TEFs). It has been shown that in the absence of costly measurements of dioxin-like polychlorinated biphenyls (dl-PCBs) in fish, relatively inexpensive measurements of total PCB can be utilized to estimate dl-PCB–related TEQ (i.e., $TEQ_{dl\text{-}PCB}$). The present study assesses the impacts of uncertainties in dl-PCB measurements and estimates, and mammalian TEFs on $TEQ_{dl\text{-}PCB}$ using the Monte Carlo technique. The analysis suggests that measurement errors for dl-PCBs translate into up to 1.3-fold uncertainty in $TEQ_{dl\text{-}PCB}$, while uncertainties in estimates of dl-PCBs generally produce up to a threefold uncertainty in $TEQ_{dl\text{-}PCB}$. In contrast, the uncertainty due to TEFs normally ranges 10- to 13-fold and spans over 30- to 40-fold under extreme cases. For 2005 TEFs, PCB-126 is the dominating contributor to uncertainty in $TEQ_{dl\text{-}PCB}$. When we considered uncertainties in the TEFs and estimated dl-PCB concentrations simultaneously, there was little increase in uncertainty in $TEQ_{dl\text{-}PCB}$ that was already produced by the TEFs only. These results indicate that the dl-PCB composition in fish and/or the relationship between total PCB and $TEQ_{dl\text{-}PCB}$ can be utilized to estimate $TEQ_{dl\text{-}PCB}$ with reasonable confidence.

Keywords—Dioxin-like polychlorinated biphenyls Dioxins/furans Toxic equivalent Uncertainty Probabilistic risk analysis

INTRODUCTION

Dioxin-like compounds (e.g., dioxins, furans, and dioxin-like polychlorinated biphenyls [dl-PCBs]) generally use the same mechanism for producing toxic/biological effects; however, their toxicity potentials and levels in fish vary by orders of magnitude [1]. The overall toxicity potential of such a mixture is expressed as a single number using the concept of toxic equivalent (TEQ). The TEQ scheme weighs toxicity of a dioxin-like compound as a fraction of the toxicity of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (2,3,7,8-TCDD), the most toxic chemical of the group. Each compound is assigned a toxic equivalency factor (TEF) that indicates the degree of toxicity compared to a reference value of 1 for 2,3,7,8-TCDD. The concentration of a dioxin-like mixture that is toxicologically equivalent to 2,3,7,8-TCDD is then calculated by summing the multiplication of the concentration of each compound with compound-specific TEF, as shown in Equations 1 and 2 [2]:

$$TEQ = TEQ_{dl\text{-}PCB} + TEQ_{dioxin} + TEQ_{furans} \quad (1)$$

$$TEQ = \sum (TEF_{dl\text{-}PCB_i} \cdot C_{dl\text{-}PCB_i}) + \sum (TEF_{dioxin_j} \cdot C_{dioxin_j}) + \sum (TEF_{furans_k} \cdot C_{furans_k}) \quad (2)$$

where C is concentration and i, j, and k are congeners of dl-PCBs, dioxins, and furans, respectively.

Two types of congener-specific information are required for a TEQ assessment: TEFs and concentrations. Initially, TEFs were assigned by the North Atlantic Treaty Organization as international-TEFs [3,4]. More recently, the World Health Organization (WHO) suggested modified WHO-TEF (also known as TEF) [1,2]. The TEFs are point estimates that have been selected by a WHO expert panel using the measured relative potencies (REPs) as a guide. These REP values for individual congeners range from a few-fold to over five orders of magnitude. Further, the level of conservatism adopted while selecting the TEF from the REP distribution varies widely among the congeners. As such, significant uncertainty in TEQ estimates can be introduced by the use of point estimate TEFs. However, the approach is still considered the most plausible and feasible for risk assessment of halogenated aromatic hydrocarbons with dioxin-like properties [1].

The use of the REP distributions, rather than point estimate TEFs, has been recommended to evaluate the variability and uncertainty in the risk estimates [5]. At the same time, it has been argued that the use of REP distributions instead of TEFs may pose difficulties in internationally harmonizing the approach among the regulatory authorities [1]. Furthermore, lumping all REP data together without considering the differences in the studies (e.g., in vivo, in vitro) is not appropriate. However, such problems can be resolved by, for example, separating in vivo and in vitro data and/or providing a differential weighting scheme to account for the differences in data types [5].

Dioxin-like compounds are generally found in the environment at low parts-per-trillion (ppt) but at toxicologically relevant levels. Therefore, measuring concentrations of dioxin-like compounds requires high-resolution instruments and methods and is a costly process. This limits the numbers of samples that can be analyzed on a regular basis, resulting in

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uncertainty in the exposure assessment [6–8]. Alternatively, simplified approaches that have been developed to estimate concentrations of dioxin-like compounds can be utilized as practical tools. For example, Bhavsar et al. [9] recently presented regression models that allow the estimation of dl-PCB concentrations in fish from relatively inexpensive total PCB measurements. Similarly, an immunoassay method can be used to quantify $TEQ_{dioxins/furans}$ in fish [10,11]. However, the impact of uncertainties embedded in these estimates on calculated TEQ is unclear.

The present study examines uncertainty in estimates of $TEQ_{dl\text{-}PCB}$ in fish due to the variability in congener-specific mammalian REPs, use of mammalian TEFs instead of REP distributions, and use of the estimated dl-PCB concentrations from the composition presented by Bhavsar et al. [9] in the absence of measured dl-PCB concentrations. We focus on dl-PCBs because they are generally the greatest contributors to overall TCDD equivalent TEQ [12–14]. Mammalian TEFs, as opposed to fish or bird TEFs, were used because our aim was to assess risk to fish-eating humans rather than to fish themselves. Although TEFs have been revised recently (i.e., TEF-2005), we also include previous TEFs (i.e., TEF-1998) in the uncertainty analysis because of their previous widespread use [1,2]. Similarly, we considered both REP-1997 and REP-2004 data sets from which the respective old (TEF-1998) and new (TEF-2005) TEFs were selected. Furthermore, we consider geometric mean REPs (geomean-REPs) to examine the impact of using these values instead of the panel-picked TEFs. However, the inclusion of geomean-REPs was for comparison purpose only, and we are not advocating the use of geomean-REP values for TEQ estimation. The analysis is conducted in three steps: uncertainty due to dl-PCB estimates only, TEFs/geomean-REPs only, and combined dl-PCB estimates and TEFs. This is achieved by first deriving reference multiplier values that are linearly related to $TEQ_{dl\text{-}PCB}$ and then examining the variations in these multipliers that reflect possible $TEQ_{dl\text{-}PCB}$ distribution for a given total PCB concentration as described in the *Materials and Methods* section.

MATERIALS AND METHODS

Derivation of multipliers

A linear relationship between $TEQ_{dl\text{-}PCB}$ and total PCB in fish has been reported by Bhavsar et al. [15]. The relationship was attributed to the relatively stable composition of dl-PCBs in fish. A similar relationship (Eqns. 6 and 7) can be formulated using the fractions of each dl-PCB in total PCB as described here:

$$TEQ_{dl\text{-}PCB} = \sum_{i=1}^{12} (C_i \cdot TEF_i) \tag{3}$$

where C_i is the concentration of dl-PCB congener i.

$$TEQ_{dl\text{-}PCB} = \frac{\sum_{i=1}^{12} (C_i \cdot TEF_i)}{C_T} \cdot C_T \tag{4}$$

where C_T is total PCB concentration.

$$TEQ_{dl\text{-}PCB} = \sum_{i=1}^{12} \left(\frac{C_i}{C_T} \cdot TEF_i\right) \cdot C_T \tag{5}$$

$$TEQ_{dl\text{-}PCB} = \sum_{i=1}^{12} (v_i \cdot TEF_i) \cdot C_T \tag{6}$$

where v_i is the fraction of dl-PCB congener i in total PCB. The term $\Sigma_{i=1}^{12} (v_i \cdot TEF_i)$ can be converted into a constant value depending on the values selected for v_i and TEF_i. We call this constant value multiplier M. Therefore,

$$TEQ_{dl\text{-}PCB} = M \cdot C_T \tag{7}$$

Because $TEQ_{dl\text{-}PCB}$ is a linear function of M, any change in M would result in the same variation in estimated $TEQ_{dl\text{-}PCB}$. This characteristic provides an opportunity to study the impact of uncertainties in v_i and/or TEF_i on the multiplier M and thereby on the estimates of $TEQ_{dl\text{-}PCB}$.

Selection of v_i and TEFs/REPs

To study the impact of uncertainties in v_i, we used the dl-PCB composition reported by Bhavsar et al. [9]. Bhavsar et al. [9] analyzed what is likely the largest fish data set of dl-PCB and total PCB generated by the Ontario Ministry of the Environment. The data set included measurements of total PCB and dl-PCBs in 912 skinless fillet samples of 22 different fish species collected between 1996 and 2004 from 80 locations across the province of Ontario (Canada) and varied widely in size, total PCB content, and source of PCBs. They provided relationships for concentration of each individual dl-PCB congener with total PCB concentration in fish. In addition, an average composition of dl-PCBs in total PCB was presented. Such a composition can be readily utilized to estimate concentrations of dl-PCBs from relatively inexpensive measurements of total PCB in fish. However, there is an uncertainty associated with such an estimate due to natural variability. In this uncertainty analysis, we considered mean values for v_i and their standard deviations (SD) (Table 1) [9]. We examined the distribution of v_i data points using the chi-square goodness-of-fit test using @Risk® software (@RISK Professional Ver. 4.5, Palisade, Ithaca, NY, USA), which runs in the Microsoft Excel® environment (Microsoft, Redmond, WA, USA). For most congeners, the lognormal or log-logistic distribution type is the best fit. Considering that $v_{PCB\text{-}126}$ has the highest influence on $TEQ_{dl\text{-}PCB}$ among all v_i (as discussed in the *Results* section) and has lognormal distribution, we selected lognormal distribution for all v_i.

The fractions v_i were used in conjunction with the mammalian TEFs proposed by the WHO in 1998 and 2005 [1,2] (Table 1). The impact of uncertainty in the mammalian TEFs on $TEQ_{dl\text{-}PCB}$ was studied by using the REP distributions (i.e., REPs-1997 and REPs-2004) that were considered by the WHO expert panel when selecting the TEFs in the years 1998 and 2005, respectively. The weighted geomean-REP-1997 values and their SD were adopted from Finley et al. [5] (Table 1). Similarly, geomean-REP-2004 values and their SD were calculated from the supporting information of Haws et al. [16] (Table 1). We did not use any weighting scheme to generate geomean-REP-2004 values from raw data because, to our knowledge, there is no consensus on such a scheme at present. Such a quantitative weighting scheme, which will refine and extend the preliminary weighting scheme used by Finley et al. [5], is being developed [17]. It should be noted that REPs were used only to assess the impact of uncertainty associated with the TEFs on TEQ estimates, and the quality of the REP databases is not evaluated in the present study.

Finley et al. [5] tested the fit of various types of statistical distributions of REPs-1997, including lognormal, normal, beta, and Weibull distributions The tests indicated that the lognormal distribution was the best fit for almost all congeners. Haws et

Table 1. Fractions (ν) of individual dioxin-like polychlorinated biphenyl (dl-PCB) in total PCB [9], standard deviations (SD) of the fractions [9], weighted geometric mean of relative potency (REP) values compiled in 1997 (geomean-REP-1997) [5], SD of REP-1997 [5], geometric mean of REPs compiled in 2004 (geomean-REP-2004) [16], SD of REP-2004 [16], mammalian toxic equivalency factors (TEF) recommended by the World Health Organization in 1998 (TEF-1998) [2], and mammalian TEFs recommended by the World Health Organization in 2005 (TEF-2005) [1]

dl-PCBs	ν	SD ν	Geomean-REP-1997	SD REP-1997	Geomean-REP-2004	SD REP-2004	TEF-1998	TEF-2005
PCB-077	0.00071	0.00089	0.0047	0.012	0.0011	0.091	0.0001	0.0001
PCB-081	0.00005	0.00006	0.0003	0.005	0.019	0.15	0.0001	0.0003
PCB-105	0.019	0.013	0.0005	0.002	0.00008	0.014	0.0001	0.00003
PCB-114	0.0014	0.0013	0.0046	0.0079	0.00048	0.0008	0.0005	0.00003
PCB-118	0.049	0.032	0.0009	0.0043	0.00005	0.018	0.0001	0.00003
PCB-123	0.0020	0.0015	0.0003	0.0004	0.00005	0.00028	0.0001	0.00003
PCB-126	0.00027	0.00018	0.11	0.13	0.08	0.19	0.1	0.1
PCB-156	0.0063	0.0049	0.0012	0.0043	0.00027	0.128	0.0005	0.00003
PCB-157	0.0015	0.0011	0.0027	0.0049	0.00029	0.00074	0.0005	0.00003
PCB-167	0.0034	0.0025	0.0002	0.0003	0.00002	0.00028	0.00001	0.00003
PCB-169	0.00004	0.00004	0.03	0.12	0.008	0.24	0.01	0.03
PCB-189	0.00077	0.00058	0.0001	0.0001	0.00002	0.00007	0.0001	0.00003

al. [17] performed a preliminary distributional fit analysis on the REPs-2004 and concluded that the distributions for the congeners with more than 10 REP data points did not follow any specific statistical distribution. According to our chi-square goodness-of-fit test using @Risk software, log-logistic is one of the best fits for the $REP_{PCB\text{-}126}$-2004. Considering the similarities between the lognormal and log-logistic distributions and adoption of the lognormal distribution for REPs-1997, we used the lognormal distribution for all REPs-2004. However, it should be noted that the lognormal distribution provides a little narrow spread of the data points compared to the log-logistic distribution, which may underestimate the spread of uncertainty in $TEQ_{dl\text{-}PCB}$ from TEFs, depending on the fitted parameters.

Uncertainty analysis

We calculated four reference M values for combinations of mean ν_i with each of geomean-REP-1997, geomean-REP-2004, TEF-1998, and TEF-2005 (Table 2). These values are 1.08×10^{-4}, 3.07×10^{-5}, 3.94×10^{-5}, and 3.10×10^{-5}, respectively. The @RISK software (@Risk Professional, Ver 4.5, Palisade, Ithaca, NY, USA) was then used to generate 10,000 combinations of ν_i and TEFs/geomean-REPs per model run using the Monte Carlo technique. The technique, which randomly draws values from the distribution of uncertainty defined for each variable, has been used for extended uncertainty analyses in public health risk assessments [18]. The hundreds or thousands of combinations of input values prepared using the Monte Carlo technique are used to generate a distribution for the output variable. Such a distribution can be used to judge the uncertainty associated with the output value. We used 10,000 combinations per model run throughout the present study to ensure convergence and stability of the output distributions [18,19].

The impact of uncertainty in individual ν_i values on $TEQ_{dl\text{-}PCB}$ was studied by varying ν_i according to their lognormal distributions for one dl-PCB congener at a time (i.e., 12 model runs) (Fig. 1A). We also varied ν_i for all dl-PCBs together (i.e., one model run) to examine combined effects of uncertainties in all ν_i (Fig. 1A). In this model run, the $\nu_{PCB\text{-}126}$ was varied according to its lognormal distribution, and the other ν_i were varied using their relationships with $\nu_{PCB\text{-}126}$

Table 2. Calculation of multipliers, M (unitless), using values from Table 1, that is, fractions (ν) of individual dioxin-like polychlorinated biphenyl (dl-PCB) in total PCB [9], weighted geometric mean of relative potency (REP) values compiled in 1997 (geomean-REP-1997) [5], geometric mean of REPs compiled in 2005 (geomean-REP-2004) [16], mammalian toxic equivalency factors (TEF) recommended by the World Health Organization in 1998 (TEF-1998) [2], and mammalian TEF recommended by the World Health Organization in 2005 (TEF-2005) [1]. Percentage contribution of each individual dl-PCB to dl-PCB–related toxic equivalent concentration ($TEQ_{dl\text{-}PCB}$) was calculated as $(\nu_i \cdot TEF_i)/\Sigma(\nu_i \cdot TEF_i) \cdot 100$

	$\nu_i \cdot TEF_i$				% Contribution to $TEQ_{dl\text{-}PCB}$			
dl-PCB congener	ν·Geomean-REP-1997	ν·Geomean-REP-2004	ν·TEF-1998	ν·TEF-2005	Geomean-REP-1997	Geomean-REP-2004	TEF-1998	TEF-2005
PCB-077	3.3×10^{-6}	8.0×10^{-7}	7.1×10^{-8}	7.1×10^{-8}	3.07	2.60	0.18	0.23
PCB-081	1.6×10^{-8}	1.0×10^{-6}	5.2×10^{-9}	1.6×10^{-8}	0.01	3.28	0.01	0.05
PCB-105	9.6×10^{-6}	1.5×10^{-6}	1.9×10^{-6}	5.8×10^{-7}	8.90	4.78	4.88	1.86
PCB-114	6.6×10^{-6}	6.9×10^{-7}	7.2×10^{-7}	4.3×10^{-8}	6.09	2.23	1.82	0.14
PCB-118	4.4×10^{-5}	2.6×10^{-6}	4.9×10^{-6}	1.5×10^{-6}	41.05	8.37	12.50	4.77
PCB-123	6.1×10^{-7}	9.7×10^{-8}	2.0×10^{-7}	6.1×10^{-8}	0.57	0.32	0.52	0.20
PCB-126	3.0×10^{-5}	2.2×10^{-5}	2.7×10^{-5}	2.7×10^{-5}	27.63	70.18	68.85	87.61
PCB-156	7.5×10^{-6}	1.7×10^{-6}	3.1×10^{-6}	1.9×10^{-7}	6.99	5.51	7.98	0.61
PCB-157	4.1×10^{6}	4.4×10^{-7}	7.7×10^{-7}	4.6×10^{-8}	3.83	1.42	1.94	0.15
PCB-167	6.9×10^{-7}	5.6×10^{-8}	3.4×10^{-8}	1.0×10^{-7}	0.64	0.18	0.09	0.33
PCB-169	1.2×10^{-6}	3.3×10^{-7}	4.1×10^{-7}	1.2×10^{-6}	1.14	1.07	1.04	3.97
PCB-189	7.7×10^{-8}	1.8×10^{-8}	7.7×10^{-8}	2.3×10^{-8}	0.07	0.06	0.20	0.07
Total	1.08×10^{-4}	3.07×10^{-5}	3.94×10^{-5}	3.10×10^{-5}	100.0	100.0	100.0	100.0
			$\Sigma(\nu_i \cdot TEF_i) = M$					

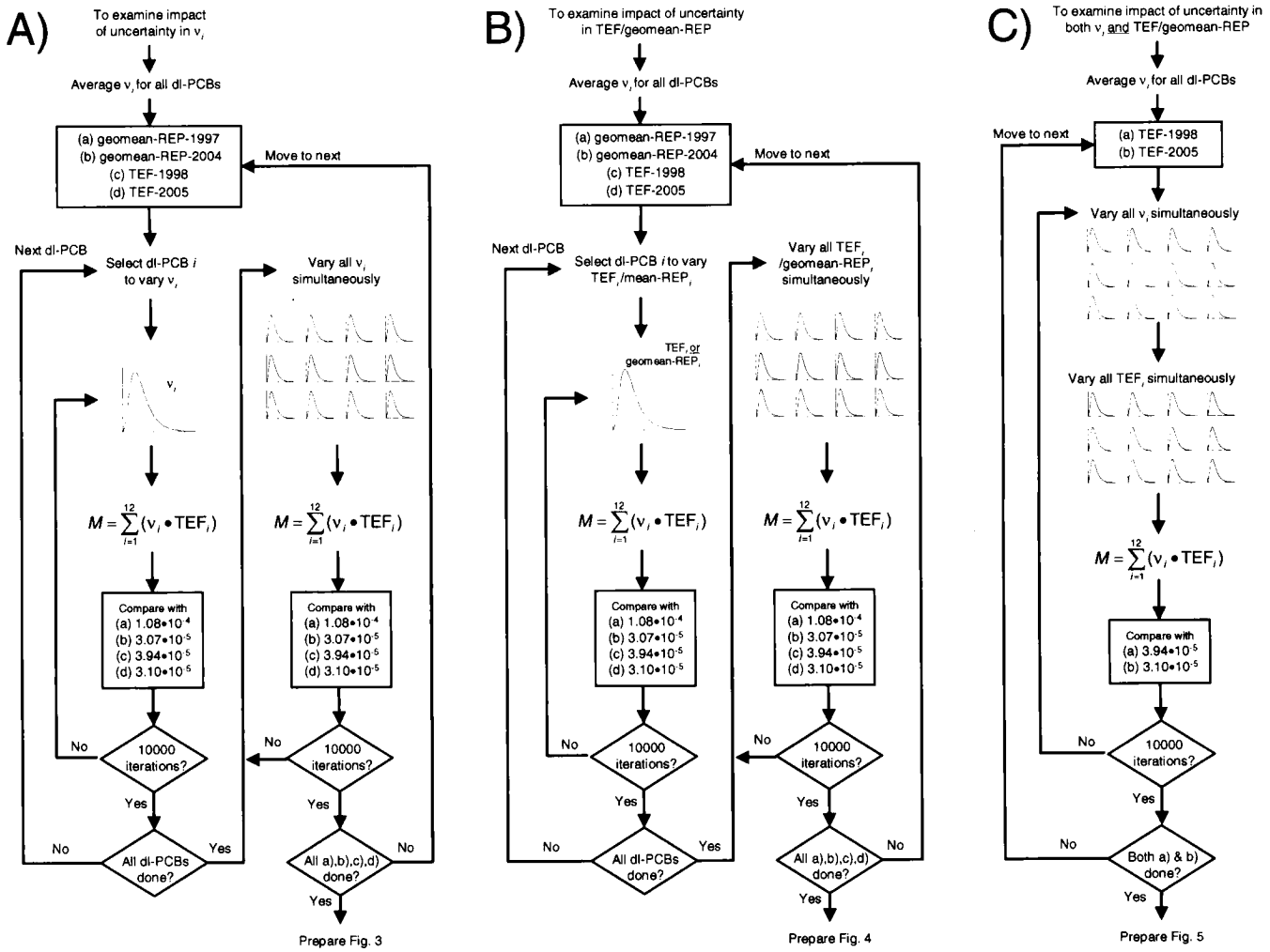

Fig. 1. Schematic presentation of the Monte Carlo analysis to assess impacts of uncertainties in (**A**) estimates of dioxin-like polychlorinated biphenyls (dl-PCBs), (**B**) toxic equivalency factors (TEFs)/geomean of relative potencies (geomean-REPs), and (**C**) both estimates of dl-PCBs and TEFs on dl-PCB–related toxic equivalent. The numbers (e.g., 1997, 2005) represent years in which REP database or TEF values were published.

as shown in Figure 2. These relationships were prepared using v_i data points following Bhavsar et al. [9]. The total 13 model runs produced 10,000 M values per run for each of geomean-REP-1997, geomean-REP-2004, TEF-1998, and TEF-2005. The assessment of variation in these M values compared to the respective reference M values quantifies uncertainties in M and thereby $TEQ_{dl\text{-}PCB}$ due to uncertainties in dl-PCBs estimated from the v_i reported by Bhavsar et al. [9] (Table 1).

In order to assess uncertainty in $TEQ_{dl\text{-}PCB}$ due to uncertainties in each of geomean-REP-1997, geomean-REP-2004, TEF-1998, and TEF-2005, we used a similar process to generate 10,000 M values per model run for combinations of mean v_i with TEFs/geomean-REPs, where TEFs/geomean-REPs were varied according to the lognormal distributions of the REPs from which they were selected (Fig. 1B). Similarly to the previous analysis, the runs included varying TEFs/geomean-REPs for one dl-PCB congener at a time (i.e., 12 runs) as well as for all dl-PCBs together (i.e., one run) for each of geomean-REP-1997, geomean-REP-2004, TEF-1998, and TEF-2005 (Fig. 1B). When all TEFs/geomean-REPs were varied simultaneously, they were assumed to be independent of one another. The assessment of variation in these M values compared to the respective reference M values (Table 2), quantifies uncertainties in M and thereby $TEQ_{dl\text{-}PCB}$ due to uncertainties in TEFs/geomean-REPs. As shown in Figure 1C, we also varied both v_i and TEFs for all dl-PCBs together to examine the overall impact of uncertainties in estimated dl-PCB concentrations and TEFs on $TEQ_{dl\text{-}PCB}$. We report the uncertainty results as expected variation in the estimated $TEQ_{dl\text{-}PCB}$ on 5th- and 95th-percentile basis.

RESULTS AND DISCUSSION

Uncertainty due to dl-PCB estimates

We start this analysis with geomean-REPs, as these values would be a logical choice in the absence of any panel-picked TEFs. First, geomean-REPs-1997 were used, and v_i were varied for each dl-PCB individually as well as simultaneously (Fig. 1A-a). As shown in Figure 3A, uncertainties in $v_{PCB\text{-}118}$ and $v_{PCB\text{-}126}$ produce the highest (up to 1.3- and 1.5-fold, respectively) uncertainty in the reference M value (1.08×10^{-4}) and thereby $TEQ_{dl\text{-}PCB}$. The individual uncertainty in v of PCB-105, -114, -156, and -157 produces up to 1.1-fold uncertainty in $TEQ_{dl\text{-}PCB}$. The uncertainties in the rest of the v_i have negligible impact on $TEQ_{dl\text{-}PCB}$ estimates. This congener-specific impact on $TEQ_{dl\text{-}PCB}$ is a combined effect of uncertainty in the estimate of a particular dl-PCB and its contribution to overall $TEQ_{dl\text{-}PCB}$. A congener that has higher uncertainty in its esti-

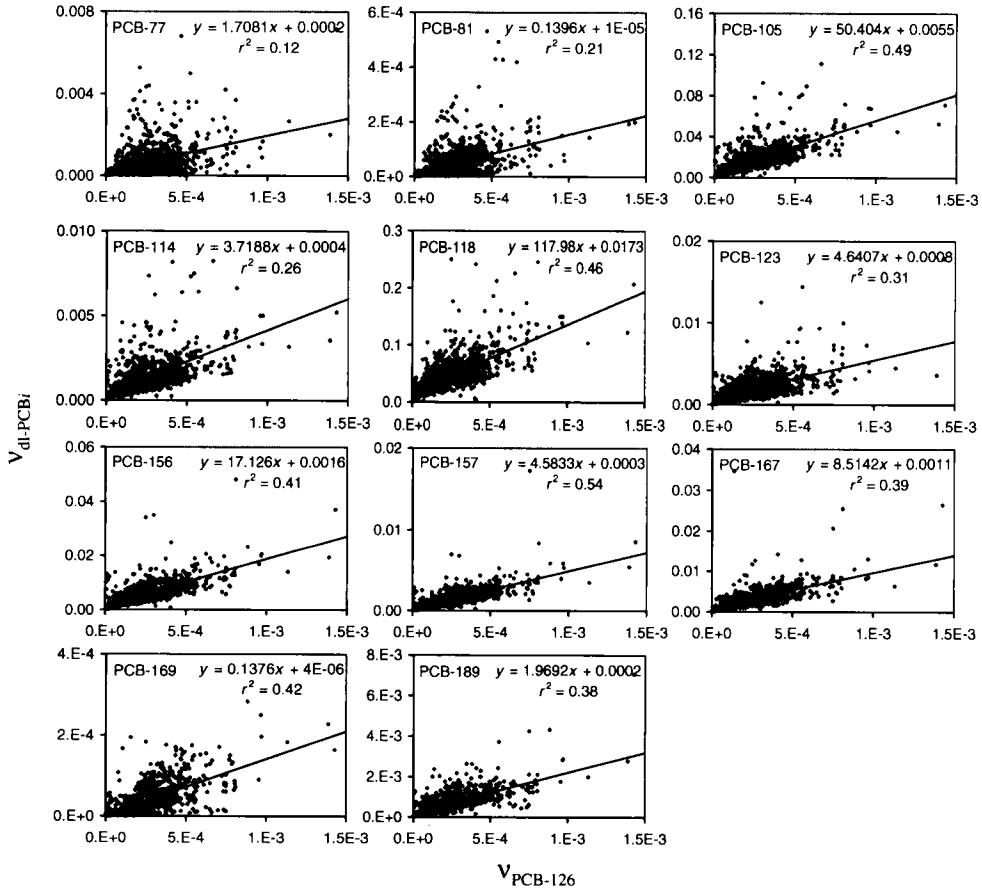

Fig. 2. Fractions of dioxin-like polychlorinated biphenyls (dl-PCBs) in total PCB ($v_{dl\text{-}PCB_i}$) as a function of the fraction of PCB-126 in total PCB ($v_{PCB\text{-}126}$). The graphs are prepared for the sample size (n) of 912 using the Ontario Ministry of the Environment data discussed by Bhavsar at al. [9]. Statistical significance (p) for all regressions is <0.001. The x is $v_{PCB\text{-}126}$, y is $v_{dl\text{-}PCB_i}$ for congener i, and r^2 is coefficient of determination.

mated concentration and has greater contribution to $TEQ_{dl\text{-}PCB}$ would produce greater uncertainty in $TEQ_{dl\text{-}PCB}$. When we use geomean-REPs-1997, PCB-118 and -126 contribute, on average, approximately 41 and 28% to $TEQ_{dl\text{-}PCB}$, respectively (Table 2). The highest contributions of these congeners to $TEQ_{dl\text{-}PCB}$ and higher uncertainties in their v_i values (refer to SD v; Table 1) make them the greatest contributors to uncertainty in $TEQ_{dl\text{-}PCB}$.

Next, to evaluate uncertainty due to the use of geomean-REP-2004, the procedure of the first step was repeated in the

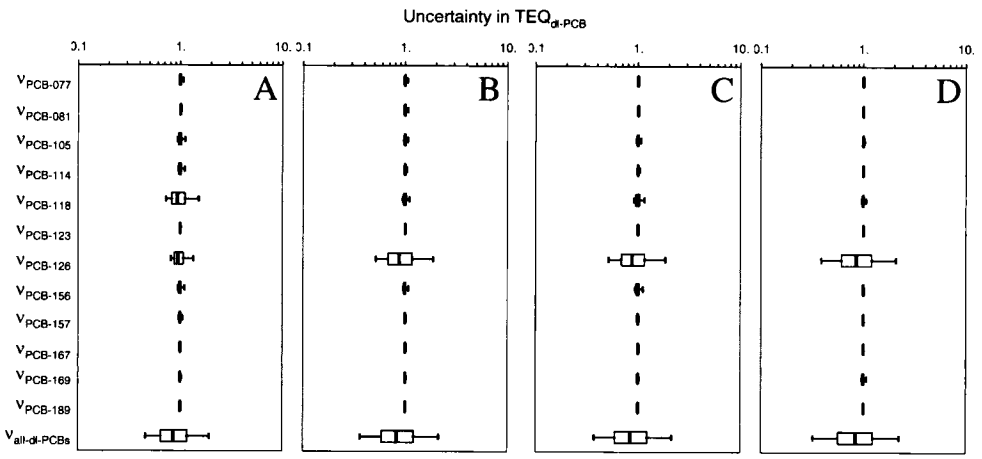

Fig. 3. Uncertainty in M values, and thereby dioxin-like polychlorinated biphenyl (dl-PCB)–related toxic equivalent ($TEQ_{dl\text{-}PCB}$), due to uncertainty in fractions of dl-PCBs in total PCB ($v_{dl\text{-}PCBs}$). The results are presented as ratios of M values estimated by varying fraction of, first, individual dl-PCB and then all dl-PCBs together to the respective reference M value (Table 2) estimated using mean v (Table 1). The results are compared for the use of (**A**) geometric mean of relative potencies published in the 1997 data set (geomean-REP-1997), (**B**) geometric mean of relative potencies published in the 2004 data set (geomean-REP-2004), (**C**) toxic equivalency factors published in 1998 (TEF-1998), and (**D**) TEF-2005. These results are presented on a logarithmic scale as box plots in which the line within the box indicates median, box indicates the 25th and 75th percentiles, and whiskers indicate 5th and 95th percentiles. The fractions were varied according to the lognormal distribution profiles prepared from their means and standard deviations (Table 1) using the @RISK software (@Risk Professional, Ver 4.5, Palisade, Ithaca, NY, USA).

Table 3. Illustration of uncertainty in dioxin-like polychlorinated biphenyl (dl-PCB)–related toxic equivalent concentration ($TEQ_{dl\text{-}PCB}$) (based on toxic equivalency factors recommended by World Health Organization in 1998; TEF-1998) due to errors in the dl-PCB measurements in biota. Percentage contribution of each dl-PCB to $TEQ_{dl\text{-}PCB}$ (i.e., % to TEQ) taken from Table 2; individual $TEQ_{dl\text{-}PCB_i}$ (i.e., C_i·TEF_i) calculated for final $TEQ_{dl\text{-}PCB}$ of 1.00 pg/g using % to TEQ values [2]; illustrative individual dl-PCB concentration (i.e., C_i; pg/g) calculated by dividing C_i·TEF_i with the corresponding TEF_i value; percentage errors in dl-PCB measurements [7]; low and high C_i calculated from C_i and ± % error; low and high (C_i·TEF_i) calculated using TEF-1998 and low and high C_i; and $TEQ_{dl\text{-}PCB}$ of 0.72 and 1.28 pg/g for low and high C_i, respectively, compared to the base case of $TEQ_{dl\text{-}PCB}$ = 1 pg/g indicate up to 28% uncertainty in the $TEQ_{dl\text{-}PCB}$ estimates due to errors in dl-PCB measurements

	% to TEQ	C_i·TEF_i	TEF-1998	C_i	% Error	Low C_i	High C_i	Low (C_i·TEF_i)	High (C_i·TEF_i)
PCB-077	0.18	0.0018	0.0001	18.0	14	15.5	20.5	0.002	0.002
PCB-081	0.01	0.0001	0.0001	1.3	16	1.1	1.5	0.000	0.000
PCB-105	4.88	0.0488	0.0001	488.0	71	141.5	834.5	0.014	0.083
PCB-114	1.82	0.0182	0.0005	36.3	17	30.1	42.5	0.015	0.021
PCB-118	12.50	0.1250	0.0001	1,249.9	90	125.0	2,374.8	0.012	0.237
PCB-123	0.52	0.0052	0.0001	52.0	22	40.5	63.4	0.004	0.006
PCB-126	68.85	0.6885	0.1	6.9	15	5.9	7.9	0.585	0.792
PCB-156	7.98	0.0798	0.0005	159.6	23	122.9	196.3	0.061	0.098
PCB-157	1.94	0.0194	0.0005	38.8	22	30.3	47.4	0.015	0.024
PCB-167	0.09	0.0009	0.00001	87.4	12	76.9	97.9	0.001	0.001
PCB-169	1.04	0.0104	0.01	1.0	15	0.9	1.2	0.009	0.012
PCB-189	0.20	0.0020	0.0001	19.6	17	16.2	22.9	0.002	0.002
Total	100.00	1.00						0.72	1.28

second step except the geometric means of REPs-2004, instead of REPs-1997, were used (Fig. 1A-b). Under this scenario, the $\nu_{PCB\text{-}126}$ produces the highest (up to twofold) uncertainty in the reference M value (3.07×10^{-5}) and thereby $TEQ_{dl\text{-}PCB}$ (Fig. 3B). This is attributed primarily to high (70%) contribution of PCB-126 to $TEQ_{dl\text{-}PCB}$ (Table 2), which is a combination of $\nu_{PCB\text{-}126}$ and relatively high (0.08) geomean-$REP_{PCB\text{-}126}$-2004 (Table 1).

Since $TEQ_{dl\text{-}PCB}$ estimates are generally based on TEFs instead of geomean-REPs, we use TEFs-1998 and TEFs-2005 in steps 3 and 4, respectively. When we use TEFs-1998 and vary ν_i for each dl-PCB individually (Fig. 1A-c), $\nu_{PCB\text{-}126}$ produces the greatest (up to twofold) uncertainty in $TEQ_{dl\text{-}PCB}$ (Fig. 3C). The ν of PCB-118, -105 and -156 individually produced up to 1.2-fold uncertainty in $TEQ_{dl\text{-}PCB}$. The uncertainties in the estimates of the rest of the dl-PCBs have negligible impact on $TEQ_{dl\text{-}PCB}$. For the TEFs-1998, PCB-126 is the major (69%) contributor to $TEQ_{dl\text{-}PCB}$ (Table 2), mainly because of its high TEF (0.1) compared to the TEFs (0.0001–0.0005) for other congeners (e.g., PCB-118, -115, -156) that can be present in fish at relatively greater concentrations (i.e., high ν_i; Table 2). The lower (1.2-fold) uncertainty from $\nu_{PCB\text{-}118}$ for TEFs-1998 (Fig. 3C) compared to the respective uncertainty (1.5-fold) for geomean-REP-1997 (Fig. 3A) is attributed to the nine-times-lower $TEF_{PCB\text{-}118}$-1998 (0.0001) than geomean-$REP_{PCB\text{-}118}$-1997 (0.0009) (Table 1).

A replacement of TEFs-1998 with the newer TEFs-2005 in the fourth step (Fig. 1A-d) also resulted in the highest uncertainty in $TEQ_{dl\text{-}PCB}$ from $\nu_{PCB\text{-}126}$ (Fig. 3D). This uncertainty is within 2.5-fold (Fig. 3D) and is attributed to the dominating (88%) contribution of PCB-126 to $TEQ_{dl\text{-}PCB}$ (Table 2). It should be noted that there is no difference between $TEF_{PCB\text{-}126}$-1998 and $TEF_{PCB\text{-}126}$-2005 (Table 1). The increase in contribution of PCB-126 to $TEQ_{dl\text{-}PCB}$ from 69% (for TEFs-1998) to 88% (for TEFs-2005) is due mainly to decreases in TEFs of other congeners (e.g., PCB-118, -115, -156; Table 1) that can be present in fish at relatively greater amounts (i.e., high ν_i; Table 2).

Overall, among all ν_i, $\nu_{PCB\text{-}126}$ is the major contributor to uncertainty in $TEQ_{dl\text{-}PCB}$ (Fig. 3). When we concurrently varied ν_i for all dl-PCBs, the uncertainty in M was up to threefold (Fig. 3A–D, last row). These results indicate that the $TEQ_{dl\text{-}PCB}$ estimated using the dl-PCB composition reported by Bhavsar et al. [9] and total PCB measurement is expected to be within threefold of $TEQ_{dl\text{-}PCB}$ calculated from dl-PCB measurements. It is noteworthy that even direct measurements of dl-PCBs in fish have inherent analytical errors that can range from 12 to 90% [7]. The expected uncertainties in $TEQ_{dl\text{-}PCB}$ due to such measurement errors can be up to 1.3- and 1.2-fold for TEF-1998 and TEF-2005, respectively (Tables 3 and 4). In addition, the sampling error also contributes to uncertainty in $TEQ_{dl\text{-}PCB}$ and is often difficult to assess [7]. In order to minimize the influence of such error, many more fish samples than typical sample size would have to be analyzed; however, the relatively high cost for dl-PCB fish analysis may prevent analyzing a large number of fish samples [7]. In contrast, the dl-PCB composition presented by Bhavsar et al. [9] is based on what is likely the largest fish data set of dl-PCB and total PCB and showed a very high statistical significance ($p < 0.001$).

Uncertainty due to TEFs/geomean-REPs

We assess the impact of uncertainties in mammalian TEFs/geomean-REPs on $TEQ_{dl\text{-}PCB}$ in four steps. In the first step, mean ν_i were used with geomean-REPs-1997, which were varied for each dl-PCB individually as well as simultaneously according to their lognormal distributions (Fig. 1B-a). As shown in Figure 4A, uncertainty in geomean-$REP_{PCB\text{-}118}$-1997 produces up to 2.2-fold uncertainty in the reference M value (1.08×10^{-4}) and thereby $TEQ_{dl\text{-}PCB}$; the corresponding uncertainty from geomean-$REP_{PCB\text{-}126}$-1997 is approximately 1.6-fold. The geomean-REPs-1997 for PCB-105, -114 and -156 produce approximately 1.3-, 1.2-, and 1.2-fold uncertainties, respectively. The uncertainties from the geomean-REPs-1997 for the other dl-PCBs are negligible. These congener-specific differences in the uncertainties from geomean-REPs-1997 are in accordance with their relative contributions to $TEQ_{dl\text{-}PCB}$ (e.g., PCB-118, 41%; PCB-126, 27.6%; Table 2). When we simultaneously vary geomean-REPs-1997 for all dl-PCBs, the uncertainty in $TEQ_{dl\text{-}PCB}$ is up to fivefold (Fig. 4A, last row).

Next, we repeated the procedure of the first step, except instead of using and varying geomean-REPs-1997, we used

Table 4. Illustration of uncertainty in dioxin-like polychlorinated biphenyl (dl-PCB)–related toxic equivalent concentration ($TEQ_{dl\text{-}PCB}$) (based on toxic equivalency factors recommended by World Health Organization in 2005; TEF-2005) due to errors in the dl-PCB measurements in biota. Percentage contribution of each dl-PCB to $TEQ_{dl\text{-}PCB}$ (i.e., % to TEQ) taken from Table 2; individual $TEQ_{dl\text{-}PCB_i}$ (i.e., $C_i \cdot TEF_i$) calculated for final $TEQ_{dl\text{-}PCB}$ of 1.00 pg/g using % to TEQ values [1]; illustrative individual dl-PCB concentration (i.e., C_i; pg/g) calculated by dividing $C_i \cdot TEF_i$ with the corresponding TEF_i value; percentage errors in dl-PCB measurements [7]; low and high C_i calculated from C_i and ± % error; low and high ($C_i \cdot TEF_i$) calculated using TEF-2005 and low and high C_i; and $TEQ_{dl\text{-}PCB}$ of 0.8 and 1.2 pg/g for low and high C_i, respectively, compared to the base case of $TEQ_{dl\text{-}PCB}$ = 1 pg/g indicate up to 20% uncertainty in the $TEQ_{dl\text{-}PCB}$ estimates due to errors in dl-PCB measurements

	% to TEQ	$C_i \cdot TEF_i$	TEF-2005	C_i	% Error	Low C_i	High C_i	Low ($C_i \cdot TEF_i$)	High ($C_i \cdot TEF_i$)
PCB-077	0.23	0.0023	0.0001	22.9	14	19.7	26.1	0.002	0.003
PCB-081	0.05	0.0005	0.0003	1.7	16	1.4	1.9	0.000	0.001
PCB-105	1.86	0.0186	0.00003	621.0	71	180.1	1,061.9	0.005	0.032
PCB-114	0.14	0.0014	0.00003	46.2	17	38.3	54.1	0.001	0.002
PCB-118	4.77	0.0477	0.00003	1,590.5	90	159.1	3,022.0	0.005	0.091
PCB-123	0.20	0.0020	0.00003	66.1	22	51.6	80.7	0.002	0.002
PCB-126	87.61	0.8761	0.1	8.8	15	7.4	10.1	0.745	1.008
PCB-156	0.61	0.0061	0.00003	203.1	23	156.4	249.8	0.005	0.007
PCB-157	0.15	0.0015	0.00003	49.4	22	38.6	60.3	0.001	0.002
PCB-167	0.33	0.0033	0.00003	111.2	12	97.9	124.6	0.003	0.004
PCB-169	3.97	0.0397	0.03	1.3	15	1.1	1.5	0.034	0.046
PCB-189	0.07	0.0007	0.00003	24.9	17	20.7	29.1	0.001	0.001
Total	100.00	1.00						0.80	1.20

and varied geomean-REPs-2004 (Fig. 1B-b). Under this scenario, geomean-$REP_{PCB\text{-}126}$-2004 produces the highest (up to threefold) uncertainty in $TEQ_{dl\text{-}PCB}$ (Fig. 4B). The uncertainties in geomean-REPs-2004 for the other dl-PCBs have comparatively negligible (<1.1-fold) impact on $TEQ_{dl\text{-}PCB}$. When geomean-REPs-2004 are varied for all dl-PCBs at the same time, the uncertainty in $TEQ_{dl\text{-}PCB}$ is up to 10-fold (Fig. 4B, last row).

In the third step, we used mean v_i with the TEFs-1998 and then varied TEFs-1998 for each dl-PCB individually as well as simultaneously according to the lognormal distributions of respective REPs-1997 (Fig. 1B-c). In general, the pattern of estimated uncertainties in $TEQ_{dl\text{-}PCB}$ from TEFs-1998 (Fig. 4C) is identical to the results for geomean-REPs-1997 (Fig. 4A); however, the average (not median) uncertainties are approximately 2.75-fold higher (results not shown). The similarity in the patterns is attributed to the use of the REP-1997 distributions to vary both geomean-REPs-1997 and TEFs-1998. The 2.75-fold-greater uncertainty is because of overall 2.75-fold-lower $TEQ_{dl\text{-}PCB}$ produced by the TEFs-1998 compared to the geomean-REPs-1997. This is evident from 2.75-fold-lower M value of 3.94×10^{-5} for the TEFs-1998 compared to 1.08×10^{-4} for the geomean-REPs-1997 (Table 2). Overall uncertainty in $TEQ_{dl\text{-}PCB}$ due to combined uncertainties in all TEFs-1998 spans fivefold (Fig. 4C, last row).

In the final step of the present analysis, we repeated the procedure of the third step but replaced the TEFs-1998 and REP-1997 distributions with the TEFs-2005 and REP-2004 distributions, respectively (Fig. 1B-d). The pattern of estimated uncertainties in $TEQ_{dl\text{-}PCB}$ from this step (Fig. 4D) is almost identical to the corresponding pattern for geomean-REP-2004 (Fig. 4B) because of the use of the REP-2004 distributions to vary both. The only minor difference was that the uncertainty from TEF-2005 compared to geomean-REP-2004 was on an average approximately 1% higher. This difference is consistent with the difference in M values of 3.10×10^{-5} and 3.07×10^{-5} for TEF-2005 and geomean-REP-2004, respectively (Ta-

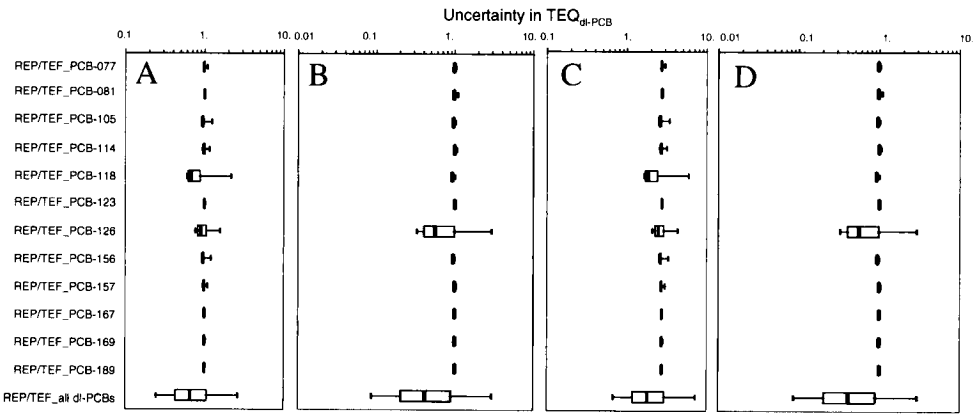

Fig. 4. Uncertainty in M values, and thereby dioxin-like polychlorinated biphenyl (dl-PCB)–related toxic equivalent ($TEQ_{dl\text{-}PCB}$), due to uncertainty in toxic equivalency factors (TEFs)/geomean of relative potencies (geomean-REPs). The results are presented as ratios of M values estimated by varying (**A** and **C**) geomean-REPs published in 1997 (geomean-REP-1997) and (**B** and **D**) geomean-REP-2004 of, first, individual dl-PCB and then all dl-PCB together to the respective reference M value (Table 2) estimated using (**A**) geomean-REP-1997, (**B**) geomean-REP-2004, (**C**) TEFs published in 1998 (TEF-1998), and (**D**) TEF-2005 (Table 1). The mean values of fractions of dl-PCBs in total PCB (v; Table 1) were used in all calculations. These results are presented on a logarithmic scale as box plots in which the line within the box indicates median, box indicates the 25th and 75th percentiles, and whiskers indicate 5th and 95th percentiles. The REP-1997 and REP-2004 were varied according to their lognormal distribution profiles prepared from their weighted geometric mean and standard deviations [5] using the @RISK software (@Risk Professional, Ver 4.5, Palisade, Ithaca, NY, USA). The TEFs were varied according to their respective REPs.

ble 2). These results (Fig. 4B and D) are parallel to the similarities and differences in the results for the TEF-1998 and geomean-REP-1997 (Fig. 4A and C). Overall uncertainty in $TEQ_{dl\text{-}PCB}$ due to combined uncertainties in all TEFs-2005 spans 10-fold (Fig. 4D, last row).

The 25th percentile of 10,000 *M* values for the simultaneous variation in TEFs-1998 of all dl-PCBs was 1.2 times the reference *M* value of 3.94×10^{-5} (Fig. 4C, last row). This suggests that the use of point-estimate TEFs-1998 instead of considering the REP-1997 distributions would underestimate $TEQ_{dl\text{-}PCB}$ in more than 75% of cases. In contrast, the 75th percentile of 10,000 *M* values for the simultaneous variation in TEFs-2005 of all dl-PCBs was 0.9 times the reference *M* value of 3.10×10^{-5} (Fig. 4D, last row). This indicates that the use of TEFs-2005 instead of considering the REP-2004 distributions provides a conservative estimate of $TEQ_{dl\text{-}PCB}$ in more than 75% of cases. However, it should be noted that the $TEQ_{dl\text{-}PCB}$ estimated using the REP distributions from the revised REP-2004 database will be lower by an average 3.5-fold compared to the REP-1997 database. This is evident from the comparison of the reference *M* values of 1.08×10^{-4} and 3.07×10^{-5} for geomean-REP-1997 and geomean-REP-2004, respectively (Table 2). Similarly, the reference *M* values of 3.94×10^{-5} and 3.10×10^{-5} for TEF-1998 and TEF-2005, respectively (Table 2), suggest that $TEQ_{dl\text{-}PCB}$ estimated using the newer TEFs-2005 will be on average 21% lower compared to the TEFs-1998. This result is in agreement with the expected approximately 16% decrease in fish TEQ_{Total} (i.e., TEQ for combined dioxins, furans and dl-PCB) from use of TEF-2005 instead of TEF-1998 [1].

Uncertainty due to combined dl-PCB estimates and TEFs

To examine the combined effects of uncertainties in estimated dl-PCB concentrations and mammalian TEFs on $TEQ_{dl\text{-}PCB}$, we varied both v_i and TEFs for all dl-PCBs simultaneously (Fig. 1C). Figure 5A and B compares the results for this analysis for TEF-1998 and TEF-2005, respectively, with the results for all v_i only and all TEFs only. The whiskers in Figure 5 also include minimum and maximum values to illustrate extreme uncertainties in $TEQ_{dl\text{-}PCB}$. The uncertainty in $TEQ_{dl\text{-}PCB}$ due to v_i only is generally (5th–95th percentiles) within two- to threefold and within 10-fold under the extreme cases (min–max values). In contrast, uncertainty due to TEFs only generally range 10- to 13-fold and spans over 30- to 40-fold under extreme cases. The uncertainty due to newer TEFs-2005 is on average 10-fold greater than for previously recommended TEFs-1998. The uncertainty in $TEQ_{dl\text{-}PCB}$ due to combined v_i and TEFs is generally the same and under extreme cases a little greater than the uncertainty due to TEFs only. This suggests that uncertainty in dl-PCB estimates adds insignificant uncertainty in $TEQ_{dl\text{-}PCB}$ estimates on what is already contributed by mammalian TEFs.

In summary, impacts of uncertainty in dl-PCB estimates and TEFs on $TEQ_{dl\text{-}PCB}$ were assessed using the Monte Carlo technique. The analysis was conducted by varying the values of the fractions of dl-PCBs in total PCB (v_i) and mammalian TEFs/geomean-REPs separately as well as simultaneously for individual congeners as well as for all congeners together. The values of TEFs were varied according to the lognormal distribution of the respective REPs from which they were panel picked [1,2]. The geomean-REPs and individual v_i were varied according to their lognormal distributions prepared using the means and SD [5,9,16]. When v_i for all congeners were varied

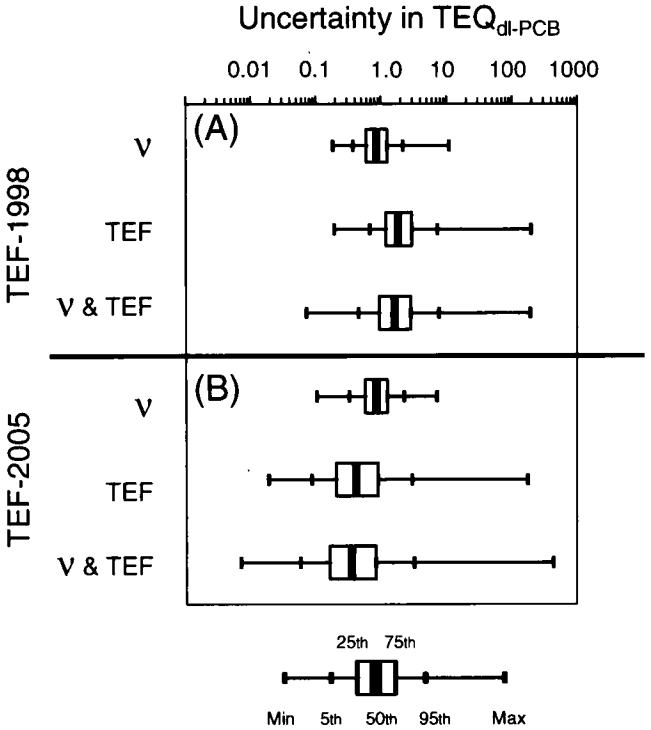

Fig. 5. Uncertainty in *M* values, and thereby dioxin-like polychlorinated biphenyl (dl-PCB)–related toxic equivalent ($TEQ_{dl\text{-}PCB}$), due to uncertainty in mean fractions of dl-PCBs in total PCB (v; Table 1), toxic equivalency factors (TEFs), and combined $v_{dl\text{-}PCBs}$ and TEFs for (**A**) TEFs published in 1998 (TEF-1998) and (**B**) TEF-2005. The results are presented as ratios of 10,000 estimated *M* values to their respective reference *M* values (Table 2) that were prepared using the TEFs and mean v (Table 1). The line within the box indicates the median, the box indicates the 25th and 75th quartiles, the inner whiskers indicate 5th and 95th percentiles, and the outer whiskers indicate minimum and maximum values.

simultaneously, the $v_{PCB\text{-}126}$ was varied according to its lognormal distribution, and the other v_i were varied using their relationships with $v_{PCB\text{-}126}$ (Fig. 2). When all TEFs/geomean-REPs were varied simultaneously, they were assumed to be independent of one another. The uncertainty in $TEQ_{dl\text{-}PCB}$ due to the errors in dl-PCB measurements [7] was also quantified.

The results presented here suggest that the measurement errors for dl-PCBs translate into up to 1.3-fold uncertainty in $TEQ_{dl\text{-}PCB}$ (Tables 3 and 4). If $TEQ_{dl\text{-}PCB}$ is estimated using total PCB measurements and the dl-PCB fractions (v_i) [9] in the absence of measured dl-PCB concentrations in fish, the uncertainty in $TEQ_{dl\text{-}PCB}$ due to uncertainty in v_i is generally within threefold for TEF-2005 (Fig. 3D). In contrast, the uncertainty in $TEQ_{dl\text{-}PCB}$ due to uncertainty in TEFs normally ranges 10- to 13-fold and spans over 30- to 40-fold in extreme cases (Figs. 4D and 5). For TEF-2005, $TEF_{PCB\text{-}126}$ and $v_{PCB\text{-}126}$ are the major contributors to uncertainty in $TEQ_{dl\text{-}PCB}$. When we considered uncertainties in the TEFs and v simultaneously, there was minimal increase in uncertainty in $TEQ_{dl\text{-}PCB}$ that was already produced by the TEFs only (Fig. 5). These results are in agreement with the findings of Smith et al. [20], who concluded that the most important factors contributing to the uncertainty in $TEQ_{dl\text{-}PCB}$ are in the order of $TEF_{PCB\text{-}126}$, sample size, and measurement uncertainty of PCB-126. This indicates that in the absence of expensive dl-PCB measurements, the dl-PCB composition in fish [9] and/or the relationship between

total PCB and $TEQ_{dl\text{-}PCB}$ [15] can be utilized to estimate $TEQ_{dl\text{-}PCB}$ with reasonable confidence.

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