CHANGE IN BACKGROUND SERUM LEVELS WITH THE NEW 2005 TEFS

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Abstract
In June of 2005 the World Health Organization met to reevaluate the toxic equivalency factors for the 29 dioxin-like compounds; TEFs for fourteen of the congeners were changed causing an expected 10 – 25% decrease in calculated TEQ for the general population. The change in the total serum TEQ is assessed for a background population in the United States using data from the University of Michigan Dioxin Exposure Study. Overall, the median serum TEQ in this population decreased by 25%; this decrease was due primarily to the down-weighting of the mono-*ortho*-substitued PCBs. The seventeen PCBs now contribute only 19% to the total TEQ in this reference population, while the dibenzo-*p*-dioxins now contribute an increased 64% to the total TEQ.

Introduction
Of the hundreds of different polychlorinated dibenzo-*p*-dioxins, dibenzofurans and polychlorinated biphenyls, only 29 are recognized by the World Health Organization (WHO) as bioaccumulating and activating the mammalian aryl hydrocarbon receptor (AhR) pathway. Because human exposure usually occurs to a mixture of these compounds, a method was developed to quantify the total AhR-activation activity present; this method compares the activity of one congener (2,3,7,8-tetrachlorodibenzo-*p*-dioxin) to the remaining 28 congeners and weights their activity appropriately, the summed activity creating a total toxic equivalency or TEQ.

In 2005 the WHO met to re-evaluate the information on the activity of these dioxin-like compounds. Though no compounds were added to or removed from the list, the estimated activity or toxic equivalency factor (TEF) of 14 congeners was changed. The authors hypothesized that the changed TEFs would reduce the total TEQ by 10% – 25%.[1,2]

The University of Michigan Dioxin Exposure Study interviewed and tested serum for dioxin-like compounds from 946 adults in Michigan, USA, including 251 individuals as part of a control population.[3] This reference population was chosen as having no unique point-source exposure to dioxins, furans or dioxin-like PCBs. The impact of the recent WHO reevaluation on serum levels in this population are presented in this paper.

Materials and Methods
Background serum data is taken from the reference population of the University of Michigan Dioxin Exposure Study (UMDES). Two counties in Michigan, USA (Jackson and Calhoun Counties) were sampled to provide comparison levels for the exposure study of three Michigan counties surrounding a Dow Chemical Plant; the comparison population had no unique point-source exposure to dioxins. Adults 18 years and older, who had lived in their current residence for five or more years were randomly selected and invited to participate. The final population-weighted sample of 251 individuals who donated blood was 95% white and 62% female with a mean age of 50 years and a mean BMI of 29 kg/m^2.

Serum samples were analyzed by Vista Analytical (El Dorado Hills, California, USA) for serum lipids and the 29 dioxin-like congeners recognized by the World Health Organization. *All results presented are lipid adjusted and population weighted.* Results falling below the limit of detection were estimated using the LOD/$\sqrt{2}$. Toxic equivalency factors used in calculations are indicated as necessary.

Results and Discussion
Table 1 lists the 14 dioxin-like congeners updated by the WHO during the 2005 reevaluation; TEFs from both the

1998 and 2005 evaluations are provided for comparison purposes. All congeners that previously had a half-order TEF on the linear scale were adjusted to a logarithmic scale (e.g. see the two pentafurans); OCDD and OCDF were both up-weighted slightly from 0.0001 to 0.0003. Two coplanar PCBs were also slightly increased. However most striking is the down-weighting of the majority of mono-ortho PCBs by a full tenth unit (PCB 167 is the only exception). Median congener concentrations from the UMDES reference population serum data are also provided in Table 1, both raw and WHO-TEF_{05} weighted.

Table 1: Weights and Median Concentrations for the 14 Congeners with Updated TEFs

	TEF		Reference Serum Data (ppt)	
	WHO 1998	WHO 2005	Median Concentration	2005 TEF-Weighted
Chlorinated dibenzo-p-dioxins				
OCDD	0.0001	0.0003	249.0	0.075
Chlorinated dibenzofurans				
1,2,3,7,8-PeCDF	0.05	0.03	0.4	0.012
2,3,4,7,8-PeCDF	0.5	0.3	5.4	1.6
OCDF	0.0001	0.0003	2.0	0.0006
Non-ortho-substituted PCBs				
PCB 81	0.0001	0.0003	1.3	0.00039
PCB 169	0.01	0.03	20.0	0.6
Mono-ortho-substituted PCBs				
PCB 105	0.0001	0.00003	1460.0	0.044
PCB 114	0.0005	0.00003	1020.0	0.031
PCB 118	0.0001	0.00003	7750.0	0.23
PCB 123	0.0001	0.00003	106.0	0.0032
PCB 156	0.0005	0.00003	8630.0	0.26
PCB 157	0.0005	0.00003	1960.0	0.0588
PCB 167	0.00001	0.00003	1350.0	0.041
PCB 189	0.0001	0.00003	530.0	0.016

With the reduced TEFs for the mono-ortho PCBs, the percent contribution of PCBs to the total TEQ has decreased. Of the seven major contributors to the serum WHO-TEQ_{98} (i.e. TCDD, PeCDD, 6-HxCDD, 2-PeCDF, PCB 126, PCB 118, PCB 156), the 2-pentafuran, PCB 118 and PCB 156 have been down-weighted. While 2,3,4,7,8-PeCDF remains a major contributor to the TEQ_{05} in the general population, both PCB 118 and PCB 156 have been dropped from the top seven (data not shown). Table 2 provides the percent contribution to the total TEQ by congener class for the UMDES reference population. As indicated above, the additional toxicity contributed by the mono-ortho PCBs has been significantly reduced, leaving the dibenzo-*p*-dioxins accounting for the majority of expected dioxin-like activity in the body.

Table 2: Percent Contribution to the TEQ_{29} by Congener Class for UMDES Reference Population

	Percent Contribution to Total TEQ	
	TEQ-WHO_{98}	TEQ-WHO_{05}
Chlorinated dibenzo-*p*-dioxins	47.3	64.0
Chlorinated dibenzofurans	17.0	16.9
Non-*ortho* substituted PCBs	9.3	14.7
Mono-*ortho* substituted PCBs	26.4	4.4
Total	100	100

Finally, Table 3 provides a comparison of the new and old TEQs by age group for the UMDES reference population. Overall, median serum TEQ levels have been reduced by 25% with the change in TEFs. This decrease ranges from about 16% in the youngest age group to 31% in the oldest group, likely reflecting the down-weighting of the increased PCB concentrations in older individuals. However the data indicates that the distribution is still heavily right-skewed.

As hypothesized, the 2005 WHO reevaluation has reduced the expected dioxin-like activity due to chlorinated compounds in the adult population by about 25%. This reduction is due almost entirely to the downgrading of the mono-ortho PCBs. With the reduction to the TEQ caused by PCBs, the percent of the TEQ contributed by dioxins has correspondingly increased.

Table 3: Comparison of 1998 and 2005 TEFs for Serum TEQ_{29} from the UMDES Reference Population

Age		$TEQ\text{-}WHO_{98}$					$TEQ\text{-}WHO_{05}$				
(yrs)	N	Min	P25	P50	P75	Max	Min	P25	P50	P75	Max
Overall	251	5.2	15.9	24.8	36.2	150.4	4.7	12.4	18.5	25.3	109
18-29	16	5.2	6.8	9.2	11.1	13.9	4.7	5.7	7.8	9.2	12.1
30-44	66	6.1	12.9	18.1	22.8	45.1	4.9	9.9	14	18.2	34.6
45-59	98	9.5	22.1	28.1	35.0	108.4	6.6	15.7	20.8	24.2	73.4
60 +	71	15.9	34.2	45.5	55.4	150.4	11.4	25.3	31.3	40.2	109

Though the impact on the current TEQ has been a net reduction, there is evidence that poly*brominated* dibenzodioxins also activate the AhR pathway. Future WHO reevaluations of TEFs and the TEQ system may once again increase the expected human body burden as new congeners are added to the currently recognized set.

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