in any of the six studies cited. It is indeed a rare epidemiologic study that has no confounders, much less an accumulated body of studies. There were, in fact, significant confounders present in most and probably all of the studies, which the authors themselves described in some detail. For example, in the three studies of welders (*7–9*), there was coexposure to nickel, a known cross-linking agent, and a variety of oxides and metal salts. As noted by Costa et al. (*7*) in their study of welders,

> ... the possible presence of confounding factors, such as smoking and diet, reported to be associated with crosslinks [*14*] does not allow a definitive conclusion.

In a preliminary report on the same study, it was noted that "...we did observe increased cross-linking but are unsure of the agent involved" (*15*). Also, as noted in the Bulgarian chrome-plater study (*6*),

> ... it is difficult to say with certainty whether the increase in DPC was due to chromium or some other chemical.

Confounding factors were also present in the "environmentally exposed" populations because their corresponding control groups were comprised in part [New Jersey (*10*)] or completely [Bulgaria (*6*)] of individuals from rural areas with significantly less industrial air pollution. In summary, we believe it is somewhat overreaching to conclude that these studies were completely free of all confounding factors.

Second, there appear to be some conflicting conclusions reached in the various studies, and we believe these warrant more discussion than given by Zhitkovich et al. (*1*). For example, in one study of welders (*7*), white blood cell DPC levels were increased over those of unexposed controls, but there was no difference in blood chromium levels between the two groups. Costa et al. (*7*) assumed *a priori* that Cr(VI) exposure had occurred and suggested that DPC may therefore be a more sensitive biomarker than blood chromium concentrations. However, in the Bulgarian chrome platers (6), blood chromium levels were significantly elevated (almost 10-fold) above controls, a clear indication that chromium exposure had occurred; yet there was no difference in DPC levels in the exposed group versus the control group. These findings are directly contradictory: DPC was elevated in workers with negative evidence of Cr(VI) exposure, and DPC was not elevated in workers with clear evidence of Cr(VI) exposure. The findings related to the "environmentally exposed" groups are also inconsistent. For example, Table 1 presented by Zhitkovich et al. (*1*) indicates that Zhitkovich et al. (*16*) measured elevated DPC in a Bulgarian population (residents of Jambol) that experienced environmental Cr(VI) exposure. However, Zhitkovich et al. (*16*) did not measure environmental Cr(VI) levels in Jambol. They simply concluded that the Jambol residents must have been exposed to Cr(VI) because their mean blood chromium level was higher than in residents from another town (Burgas). Yet this assumption is internally inconsistent with the fact that Costa et al. (*6*) found no difference in DPC levels between the chrome platers and the Jambol residents, two groups with tremendous differences in blood chromium levels. Other such inconsistencies can be found, and as a result we do not believe the epidemiologic evidence is yet sufficient to conclude that DPC is a proven biomarker for Cr(VI) exposure.

We believe that a simple, rapid, and reliable biomarker for screening or quantitating Cr(VI) exposure would be a very valuable tool. For this reason we suggest that the technical underpinnings of any proposed Cr(VI) biomarker merits rigorous evaluation before its acceptance as an accurate technique. Clearly more work should be done regarding the use of DPC to characterize exposure to Cr(VI).

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Dietary Exposure to PCBs and Dioxins

We read with great interest the paper by Patandin et al. (*1*) in which they describe their efforts to model dietary intake of certain highly lipophilic compounds (polychlorinated biphenyls and dioxins) over the first 25 years of life. In the context of exploring distributional dosimetry of breast milk contaminants to nursing children (*2*), we were particularly interested in the portion of the model that addressed intake to nursing infants. As a prerequisite of assessing potential adverse health effects, this information should be extended to estimate the resulting tissue concentrations.

For estimating tissue concentrations as a function of age, intake is one of many factors. Other factors that must be taken into account include organ and tissue volumes, as well as elimination parameters and their respective changes over time. Elimination of this class of lipophilic compounds from the body should reflect both fecal excretion of the unchanged compound and metabolism occurring mainly in the liver. Because liver and tissue volumes, as well as mass of feces, change drastically during growth, elimination parameters (represented by half-lives) cannot be time-independent constants in the range of several years, as is usually assumed. A reduced apparent half-life of

such compounds has been described in infants (*3*) and in offspring of rhesus monkeys (*4*), as exemplified by 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD). For example, the half-life for nonmetabolic elimination of TCDD has been calculated to be 0.42 years in newborns, which is substantially shorter than in adults (*3*). From TCDD data collected over more than 15 years following the Seveso incident (*5*), it is obvious that the half-life is shorter in infants and increases significantly with age.

Although the amount of TCDD in the organism is a function of uptake and elimination, the resulting tissue concentrations are also functions of the body and tissue volumes. The fast growth in the first years of life leads to a "thinning" of the TCDD tissue concentrations (*3,6*). Although the relatively fast half-life, together with the "thinning" effect, are insufficient to prevent an increase of TCDD tissue concentrations during nursing, after weaning, both growth-related dilution and elimination from the body result in a fast decrease in these concentrations. In fact, TCDD concentrations in tissues of babies breast-fed for up to 6 months can reach values in the lower range of adults, but the concentrations decline rather quickly, reaching values comparable to nonbreast-fed children at about 5 years of age (*3*). Importantly, these results are based on general assumptions related to the class of compounds described as lipophilic, nonwater soluble, nonvolatile, nonprotein bound, and either slowly metabolized or not metabolized; therefore, these results should be valid not only for TCDD but for all compounds meeting this description (*3*).

In conclusion, based on the current scientific literature, even relatively high TCDD concentrations that might be reached after 6 months of nursing do not appear to lead to a raised lifetime value. Comparing intake from breast-feeding with cumulative long-term intake may result in misleading perceptions about health risks associated with intake of TCDD and congeners.

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Patandin's Response

We would like to respond to LaKind and Filser's comments about our paper that was published in *EHP* (*1*).

LaKind and Filser emphasized that tissue concentrations of TCDD and related compounds are important when assessing potential adverse effects, rather than assessing long-term dietary intake only. We agree with them; however, long-term dietary intake is an important part of exposure assessment. In our paper we mainly focused on the polychlorinated biphenyl (PCB) and dioxin (polychlorinated dibenzodioxin and furan; PCDD/PCDF) intake during different periods in life. Over 90% of exposure to PCBs and dioxins in the general population is from oral intake. We compared the intake of toxic equivalents (TEQs) during breast-feeding (0–1 year of age), after weaning (e.g., preschool years; 1–5 years of age), and until adulthood (6–25 years of age). We also calculated the amount (percentage) of PCB/dioxin TEQ intake during a 6-month period of breast-feeding and its effect on the total cumulative intake until adulthood (25 years).

Although some model calculations of PCB/dioxin body burden and infant exposure through breast milk have been published (*2,3*), the cumulated PCB/dioxin intake from infancy until adulthood had not been quantitatively assessed. The cumulated intake as calculated in this study is not identical to body burden because losses by excretion and metabolism by the liver, as well as different half-lives of different PCB and dioxin congeners, are not taken into account (*1*). We calculated the total mean intake of PCBs/dioxins over a 25-year period in subjects who were either formula-fed or breast-fed for 3 and 6 months during infancy.

LaKind and Filser emphasized the thinning effect in infants during growth and the shorter half-lives reported for TCDD in infants. The dilution effect of PCBs and dioxins in the growing infant is a known phenomenon (*4,5*). This dilution effect is also found in older adults when the increase of PCB/dioxin tissue concentration is lower than expected because of the increase of total body fat with age (*2*).

In a previous publication (*6*), we presented the sum PCB levels (IUPAC numbers 118, 138, 153, and 180) measured in the plasma of 42-month-old children who were either breast-fed or formula-fed during infancy. The PCB levels measured at 42 months of age were strongly related ($r = 0.63$) to the period of breast-feeding and negatively associated with total body fat (percentage) and body weight. Preschool children who were breast-fed as infants have PCB body burdens that are primarily dictated by their lactational PCB exposures. The negative relationship with plasma PCB concentration and body fat percentage is most likely explained by the fact that PCBs and related compounds are distributed over all fat-containing components in the body, especially adipose tissue (diluted). Given a higher growth rate as well as this dilution effect, a shorter half-life has been reported for PCBs and dioxins in young children (*4,5*). Despite this rapid growth and shorter half-life, breast-fed infants reach PCB and dioxin levels as high as their mothers (adults) (*6*).

According to LaKind and Filser, the high TCDD tissue concentration after 6 months of breast-feeding does not give an increased lifetime value for TCDD body burden. This still needs to be investigated more thoroughly. Model calculations presented by Ayotte (*7*) show that body burden in breast-fed infants are relevant for the childhood years, but not for periods beyond 20–30 years of age. However, Smith (*8*) suggested that an infant breast-fed for 12 months would receive approximately 10% of the cumulative exposure dose per body weight that would be received by an adult with 50 years of exposure. During childhood, the body burden is raised by lactational PCB/dioxin exposure (*3,6*). At 25 years of age, the PCB/dioxin body burden could be higher due to breast-feeding for 6 months. We reported (*1*) that 6 months of breast-feeding contributes to over 10% of the cumulative dietary intake until 25 years of age. This amount of PCB/dioxin intake during 6 months of breast-feeding is not negligible and certainly will not result in misleading perceptions about health risk assessment. In this paper (*1*), we tried to give more quantitative information about the dietary intake and several body burden calculations. We want to emphasize that although PCB/dioxin accumulation in the infant's body is a disadvantage, there are numerous advantages of breast-feeding on the general development of infants; therefore, we do not encourage shortening the lactation period in the general population (*1,9*).