DIOXIN INDUCES LOWER HUMAN OFFSPRING SEX RATIO AT BIRTH THROUGH THE FATHER

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Introduction

Polychlorinated dibenzo-*p*-dioxins (PCDDs), polychlorinated biphenyls (PCBs) and polychlorinated dibenzofurans (PCDFs) are products and byproducts of industrial or combustion processes. These compounds have been identified in almost all animal species, including humans. Some of these chemicals can disrupt multiple endocrine pathways and induce a large spectrum of toxic responses depending on target organs, sex, age and species[1,2].

We have recently described[3] for the first time a strikingly lower sex ratio at birth in the offspring of people highly exposed to 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD or dioxin). The residential exposure took place in and around Seveso, Italy on July 10, 1976, as a result of an explosion at a plant manufacturing the herbicide 2,4,5-trichlorophenol (TCP).

Researchers, have recently reported a reduced proportion of male births in the general population in several industrial countries[4] and in selected populations such as in sawmill industry workers who were exposed to trichlorophenate contaminated with various dioxin congeners[5,6] and those exposed to air pollution from incinerators.[7]

The possible origin (paternal, maternal or both) of the slight excess of female births is not clear.

In view of this lack of knowledge and of the concern derived from the wide distribution of PCBs and PCDDs in the environment we have attempted to determine whether the parents' sex and/or age at exposure in 1976 in Seveso affected the sex ratio of their children.

Methods We have measured the serum TCDD levels in exposed parents (239 males and 296 females) using serum samples drawn in 1976 and 1977 and have investigated the sex of their offspring (346 females, 328 males born from 1977 to 1996).

Results and Discussion. There is an increased probability of female births (lower sex ratio) with increasing TCDD levels in the father's serum. The TCDD lowering sex ratio effect starts at levels less than 20 ng/Kgbw. The mother's serum TCDD levels and the age at conception of either the father or mother were not predictors of outcome. Exposure of males during their pre-and puberty years may be especially relevant as fathers exposed when less than 19 years of age sired significantly more girls than boys.

Our data relate a modification in the expected human sex ratio in a residential population that was clearly known to have been exposed to TCDD. We confirm our preliminary observation[3] that high serum levels of dioxin in parents strongly lower the sex ratio (increased number of females) of their offspring. In addition, we demonstrate that serum dioxin levels lower than those already shown[3] may have a similar effect, if the exposure is to the father. Father's serum TCDD levels less than 80 ppt were a significant predictor of the probability of a male birth. Mother's serum TCDD levels were not a significant predictor of the probability of a male birth.

Furthermore, exposure to males during their pre-or puberty years is linked to this sex ratio effect, as demonstrated by their offspring being predominantly female even though their offspring were conceived several years later when the father's serum dioxin levels were much less. This indicates that the pre-and pubertal years may be a very sensitive period to dioxin action in human males. Our data support the hypothesis of a permanent effect from the moment of exposure in males, who were exposed during their pre pubertal or pubertal years. This is evident by the excess of female newborns sired by these men even though they had dioxin levels less than 30 ppt, and even less than 15 ppt, at the time of conception of their offspring. We are not implying that we have evidence that serum dioxin levels of around 15 ppt lead to a decreased sex ratio. However, the evidence of this effect starts at initial TCDD levels lower than 80 ppt (lower than 16 ng/Kgbw).

The relationship of the median 1976 body burden level of dioxin (about 20 ng/Kgbw, range= 3.5-3,960 ng/Kgbw based on our serum measurements) in pre- and pubertal ages in males and the postpubertal effect on the sex ratio is in agreement with recent experimental animal data, which show a permanently altered sperm transit time through the epididymus[8,9] in adult rats exposed *in utero* and/or at lactation to mothers, who were dosed with TCDD at 64 ng/Kgbw,[8] and even at 25 ng/Kgbw.[10]

Recently, Bonduelle et al.[11] observed that the sex ratio of children born from pregnancies after intracytoplasmic sperm injection (ICSI) with testicular or epididymal spermatozoa was modified to 0.66 and 1.46, respectively.

Our finding of an altered sex ratio in the Seveso population is in agreement with the excess of females sired by fathers exposed to chlorophenates, which are known to contain traces of various dioxin congeners.[6,7]

In our study, the median body burden level in males living in 1976 in the three exposed zones, A, B, and R, was about a factor of 20 times of the average background body burden of TCDD in humans in industrialized countries.[12] The observed TCDD lowering sex ratio effect starts at levels less than 20 ng/Kgbw.

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