GENDER OF CHILDREN OF RUSSIAN CHEMICAL PRODUCERS EXPOSED TO DIOXINS

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Introduction

Studies of the human effects of dioxin-like compounds initially focussed on acute toxicity, then on carcinogenicity, and, recently have addressed the more subtle changes of altered development and reproduction. It is now recognized that the latter outcomes are the most sensitive[1,2] effects in humans with dioxin-like compounds being suspected to function as endocrine disrupters. This belief has been fortified by the report of a skewed female offspring ratio from those individuals highly exposed to 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) as a result of an accidental exposure at Seveso, northern Italy in July 1976[3]. Further study of the same cohort revealed that the effect was associated with paternal and not maternal TCDD exposure[4]. This biased gender ratio was not seen, however, in a cohort in Taiwan in 1978 who ingested high levels of the related chlorinated dibenzofurans and PCBs in a contaminated rice cooking oil- the Yucheng episode[5]. However only the exposed mothers and not the fathers could be evaluated in that study.

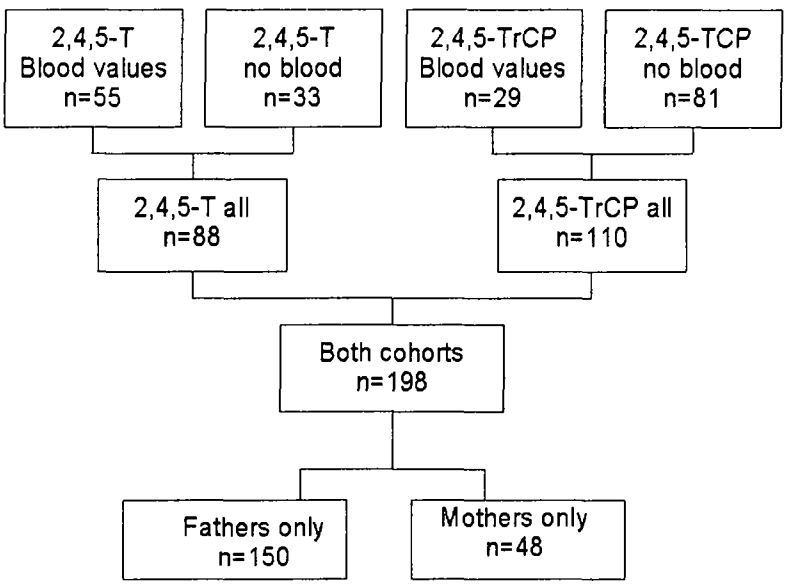
Workers who produced and were exposed to chlorinated biocides in Ufa, Baskortostan, Russia have been studied for health effects. Occupational production of the herbicide 2,4,5-trichlorophenoxyacetic acid (2,4,5-T) took place in the mid 1960s and that of the biocide, 2,4,5-trichlorophenol (TrCP) in the early 1960s to late 1980s. In light of the unbalanced sex ratio (more girls than boys) in Seveso, possibly caused by endocrine disruption due to dioxins, we report on the number of male and female children born to the Ufa workers during and subsequent to their employment in the two chemical shops. This effect on the Ufa cohort was investigated earlier[6] using only the 2,4,5-T group and a smaller number of workers. At that time the data indicated an effect similar to Seveso but the results were inconclusive. We now report on the same effect using a second related cohort and larger numbers of exposed individuals.

Methods

Cohorts: Sufficient workers and their children were available from two production shops at the factory for study. The 2,4,5-T cohort worked from late 1964 to the end of 1967 at which time production ceased and epoxy resins were produced. Of the total of about 250 workers that ever worked in this shop, some 88 (35%) have been contacted and most of these have had chloracne. In this group there were no workers younger than 21 years at first exposure. The second cohort, TCP, produced 2,4,5-TrCP between the years 1963-1988. As the second shop was in operation for a much longer period, the times of beginning and end of work for individuals were more variable. Of the total of about 600 workers in this shop, there is now data on 110 (about 20%). About 15% of the 2,4,5-T cohort and 30% of the TrCP cohort were composed of young women.

Exposure assessment Exposure of these two cohorts to chlorinated dioxins and furans was assessed by analysis of bloods by gas chromatography-mass spectrometry[7]. Blood sampling took place about 25 years post-employment for the 2,4,5-T cohort and about 10 years for the TCP cohort. Blood levels of the TCP cohort have been analysed more recently mostly by ZA. The number of analyses from the two groups are shown in the chart.

Gender Ratio
Company archival records of these individuals were consulted for age, sex, time of working in the designated shop, and number, gender, and date of birth of children. Verification of company



Russian worker cohorts

information and additional data on date of birth and gender of all live born children were obtained by interview either by personal contact or by telephone with each worker or a close relative. Background data on the number and sex of live births from the city of Ufa and the Republic of Bashkortostan were obtained from the State Regional Statistical Department of the Republic. The number and gender of live children born any time after nine months for which the worker was employed in either of the two factory shops were used for calculation. Any children born prior to the time the parent worked in the two shops were excluded from analysis. Data on any offspring who were born live but were deceased in the interim were also included. The gender ratio, or sex ratio, or fraction male (1.0<=GR=<0) is the number of males divided by the total number of children i.e. M/(M+F).

Results and Discussion
Analytical results from the 2,4,5-T cohort showed 2,3,7,8-TCDD levels more than 30 times background with significant amounts of the toxic 1,2,3,7,8-penta congener (PnCDD)[7]. GC-MS

data from the second cohort showed as high or even higher TEQ levels with a pattern dominated by high TCCD levels and again significant amounts of PnCDD. Thus both cohorts were highly exposed to dioxins in a manner similar to Seveso but with a difference that PnCDD was also present.

A total of 227 births from 198 production workers (150 fathers and 48 mothers) from both cohorts were eligible for inclusion in the study. The gender ratios (males of total births) for both cohorts were similar and showed a combined value of 0.40. This value is statistically ($P<0.001$) skewed toward girls. The actual sex ratio for both the city of Ufa and the region of Baskortostan in the same time period (1965-1990) is about 0.51. Division of the births between exposed father or mother showed the ratio increased to 0.38 for fathers only and was not different from normal (0.51) for the mothers, although the number of births for the mothers was only 39 children. The overall number of children for the male workers (71 boys and 116 girls) is shown by year of birth in the second figure. Visual inspection alone of the figure indicates a dearth of male offspring.

Both of these findings, a skewed sex or gender ratio and an association with the father and not the mother, are consistent with what has been reported in the Seveso accident[3,4]. We are unable to propose any substantial mechanism for these outcomes. It is not possible to exclude some confounding factor with the workers that could cause this skewed ratio. However, given that no such effect was noted for the mothers, we believe the existence of such a factor is not likely. In conclusion, these data add to the evidence that dioxins are reproductive toxins in humans.

Acknowledgements
The authors express their warm appreciation to Arnold Schecter. His seminal visit to Ufa in the early 1990s when he was at the State University of New York, Binghamton, was essential in the initiation of this work.

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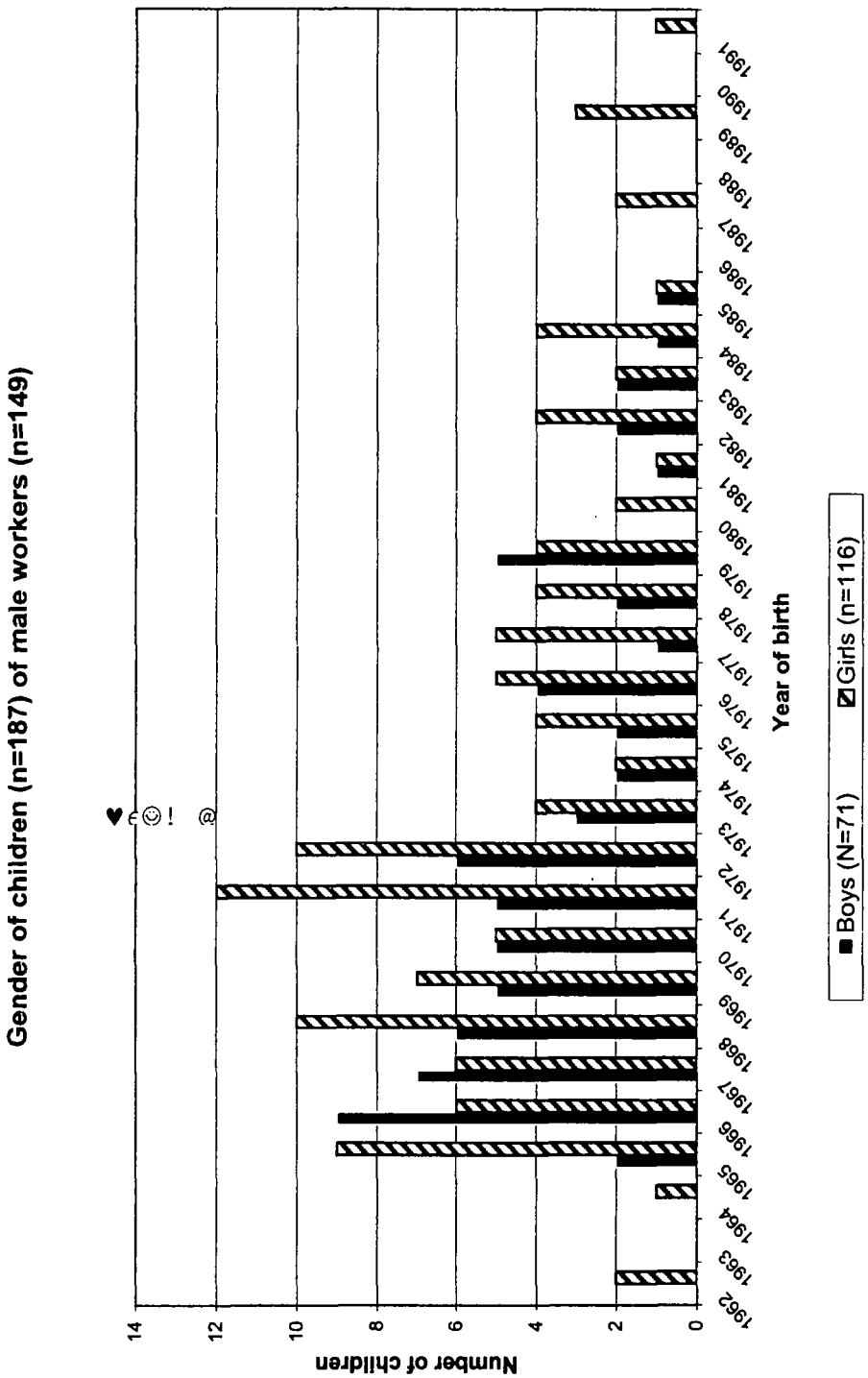
Gender of children (n=187) of male workers (n=149)
Number of children
0
2
4
6
8
10
12
14
1962
1963
1964
1965
1966
1967
1968
1969
1970
1971
1972
1973
1974
1975
1976
1977
1978
1979
1980
1981
1982
1983
1984
1985
1986
1987
1988
1989
1990
1991
Year of birth
Boys (N=71)
Girls (n=116)