DATA STORAGE ON RUSSIAN PESTICIDE PRODUCERS EXPOSED TO DIOXIN. SEX RATIOS OF THIRD GENERATION OF RUSSIAN COHORT

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Introduction

A cohort of Russian workers who produced 2,4,5-T and 2,4,5-TrCP at a chemical factory in Ufa was brought to light in the papers of A. Schecter, J. Ryan and O. Papke.[1-3]. Dioxin exposure was experimentally confirmed by PCDD/Fs determination in blood samples first for a small group of workers and their children[1]. This study permitted to connect the information of medical institutions about chloracne from which a group of young 2,4,5-T workers suffered in 1965-67 with exposure to dioxin.

Further study allowed to determine the level of exposure for 60 men, women from this factory and their children and the city of Ufa[4]. PCDD/Fs determination in blood of workers was performed by two stages. The first stage was carried out in 1992-1997 at the laboratory Health Canada, Ottawa, Canada[4], the second was performed in 1996-2002 at the laboratory of the Environmental Research Center, Ufa, Russia[5,6]. Simultaneous studies carried out by two laboratories allowed to increase the number of exposed donors and to select a group of highly exposed 2,4,5-TrCP producers among whom no cases of chloracne were registered.

For a group of 189 workers of chlorine organic production (2,4,5-T, TrCP, 2,4-D) including 94 workers with confirmed high PCDD/Fs blood level the analysis of some parameters of remote consequences resulting from PCDD/Fs exposure was made[6]. Changes in sex ratio of children of highly exposed donors and the absence of deviations from normal sex ratio in the third generation of the cohort were shown[8]. But the group of workers studied at that time consisted of 28 men and 8 women and it was too small to give reliable statistical representation, only the fact itself was stated.

One of the authors of this report participated in a detailed study of sex ratio of children of donors from two groups of the Ufa cohort with the most probable exposure (2,4,5-T and TrCP production)[7]. The group consisted of 84 donors with experimentally confirmed exposure and it was enlarged to 198 individuals due to information about the workers whose occupation was close or

similar to the donors with the known PCDD/Fs concentration in blood. In the report of J. Ryan, G. Carrier at al. it was stated that human exposure of these pesticide producers to high levels of dioxins is associated with the birth of more girls but only for paternal exposure, what corresponds to the conclusion made for the Seveso cohort but contradicts to the conclusion for US chlorphenol cohort.

At present preparatory work for epidemiological study of remote consequences for reproductive function of exposed workers of the Russian cohort (Ufa) is being completed. Accumulation of data specifying and enlarging the findings of J. Ryan et al.[7] both on the number of workers, PCDD/Fs and other POPs content in blood and on demography situation is taking place. Information on the third generation of the exposed donors was picked out.

This report presents the results of the detailed study of the third generation of the Russian cohort (247 workers, 314 children and 260 grandchildren). We also present the data on the sex ratio of the second generation for the initial group enlarged by 25% as compared with the group of workers analyzed by J. Ryan et al.[7] (198 workers and 227 children). Besides, as skewed sex ratio had earlier been stated only for paternal descendants, genealogical branches of the cohort representatives were studied.

Methods and Materials

Demography and statistical data were collected by interviewing workers, their wives and children personally or by telephone questioning. For comparison the official statistical data on the city of Ufa with the population over 1.2 million people and on the whole region (over 4 million) for the period of 1960-2002 were used. Standard methods and programs were used for data treatment.

Methods of PCDD/Fs determination were described earlier[7]. PCDD/Fs concentration is given in TEQ-WHO, pg/g of lipids.
The advantage of working with the Russian cohort is a low level of migration allowing to find 80% of former workers within the city boundaries. The difficulties in the process of data collection were as follows: a) the absence of systematic observation of the cohort representatives suitable for statistical treatment; b) low self-descriptiveness of the available data on annual medical examinations carried out during the period of work at the factory; c) irreplaceable data on PCDD/Fs exposure for 15-20% of the group due to high mortality in the cohort.

Now a database has been created containing the information about 247 workers of 2,4,5-T and TrCP production in 1961-87. The data include: a) occupational route; b) data on PCDD/Fs concentration in blood of 85 workers; c) information on the children, their sex and age; d) information on the third generation, their sex and age; e) information on death cases and death causes.

Results and Discussion

The main initial data are given in Tables 1 and 2. The total number of the chemical factory workers earlier producing 2,4,5-T and TrCP is given by the information of the factory administration. More detailed information was obtained by the workers questioning.

Table 1. **Characteristics of the cohort of Russian chemical producers**

Cohort	2,4,5-T	TrCP	Combined
Total number	> 300	>700	>1000
Introduced into the database, full information	125	122	247
Gender (M/F) of workers with full information	108/17	85/37	193/54
Mean age, years	63.2	60.3	61.8
Time after exposure, years	39	30	34.5
Number of donors with stated exposure	57	28	85

Data on the number and sex of the representatives of the second generation were obtained by questioning workers and members of their families. PCDD/Fs content in blood of children of the workers was determined while blood sampling in 1992 (n=8), individual levels are given in the report of A. Schecter et al[2]. PCDD/Fs determination in 5 individual blood samples of children of workers was performed in 1997-98 at the BREC laboratory, Ufa, and the results had never been published before.

Table 2. **The 2-nd generation (children of workers)**

Cohort	2,4,5-T	TrCP	Combined
Born during and after workers exposure	180	133	313
Number of children by gender, M/F	78/102	61/72	139/174
Mean age, years	33.4	35.9	34.6
Number of donors with stated exposure	13	-	13
2378-TCDD/TEQ-WHO, PCDD/Fs, mediana	38/56	-	38/56
Sex ratio (M/M+F) with both parents	0.43	0.45	0.44
Fathers only, number	97	63	158
Number of children by gender, M/F	67/91	45/59	112/150
Sex ratio using fathers	0.42	0.43	0.43
Mothers only, number	14	28	52
Number of children by gender, M/F	11/11	16/13	27/24
Sex ratio using mothers	0.50	0.55	0.52

As it follows from the data of Table 2, values of sex ratio for the initial sampling enlarged by 25% have changed insignificantly as compared with conclusions of the report[7] for paternal offspring only and for both parents. No changes have been found for maternal offspring but we failed to enlarge the group essentially.

The third generation of the Ufa cohort includes by now 260 children what is lower than the expected values of the index of birth rate usual for the city. This is connected with a birth rate drop after the 90s in the city, in the region and in Russia on the whole caused mainly by social factors. Tendencies of sex ratio for the third generation considerably differ from those of the second generation of the cohort. No increased female fraction is observed, moreover, a very insignificant tendency to increase of male fraction for offspring of both parents of exposed donors and for mothers is observed.

Table 3. **The 3-rd generation (grandchildren of workers)**

Cohort	2,4,5-T	TrCP	Combined
Born from parents born during and after workers exposure	184	76	260
Number of grandchildren by gender, M/F	105/79	49/27	154/106
Mean age, years	12.3	9.1	10.7
Sex ratio (M/M+F) with both parents	0.57	0.64	0.59
Fathers only, number (sons of exposed workers)	78	61	139
Number of grandchildren, M/F	57/27	35/21	92/48
Sex ratio using fathers	0.64	0.63	0.66
Mothers only, number (daughters of exposed workers)	101	72	173
Number of grandchildren, M/F	48/52	19/13	67/63
Sex ratio using mothers	0.49	0.60	0.55

The found data presented as genealogical branches allow to mark out the line ***father-son-grandson*** as significantly different from the normal sex ratio of newborns.

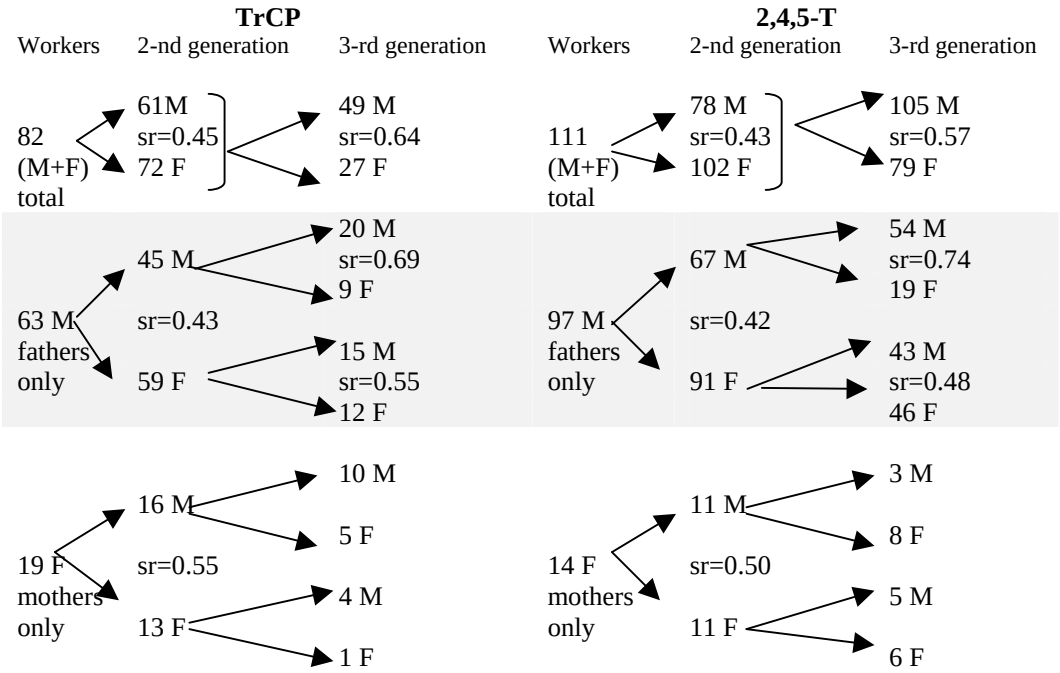

Figure 1. **Distribution of descendants of the cohort by genealogical branches**

As it follows from the data given in Tables 2,3 and Figure 1, the ratio M/M+F inconsiderably differs from normal for all groups except the line ***father-son*** in the second generation and the line ***father-son-grandson*** for the third generation. But if in the second generation this is the increase of female fraction, namely (M/M+F=112/262=0.43) what is also reflected in the general picture for the joint group of workers (M/M+F=139/311=0.45), then in the third generation the opposite picture is observed. In the third generation by paternal line more than double increase of boys number born from exposed donors is observed. For the third generation of the joint group of workers sex ratio is of normal value (M/M+F=154/260=0.59), but for the line ***father-son-grandson*** the ratio is abnormally high (M/M+F=74/102=0.74), deviation from the normal distribution makes 25-30% and is observed in both groups.

For donors with stated PCDD/Fs level in blood the data confirm already mentioned tendencies that are more distinct in TrCP group.

Table 4. **Characteristic of Russian chemical producers with experimentally stated exposure**

Cohort	2,4,5-T	TrCP	Combined
Number of donors with stated exposure	57	28	85
Gender of donors (M/F)	45/12	20/8	65/20
TEQ-WHO, PCDD/Fs (1998), mediana	179	672	243
Number and gender of children (M/F)	31/47	12/28	43/75
Sex ratio of 2-nd generation, both parents	0.39	0.28	0.36
Number and gender of children, fathers only (M/F)	24/40	6/24	30/64
Sex ratio of 2-nd generation, fathers only	0.37	0.20	0.31
Number and gender of children, mothers only (M/F)	7/7	6/4	13/11
Sex ratio of 2-nd generation, mothers only	0.5	0.6	0.54
Number and gender of grandchildren, fathers only (M/F)	34/22	11/7	45/29
Sex ratio of 3-rd generation, fathers only	0.6	0.64	0.62
Number and gender of children, mothers only (M/F)	6/7	8/4	14/11
Sex ratio of 3-rd generation, mothers only	0.46	0.66	0.56

The found data confirm the conclusions made in the report[6] on the change of normal sex ratio of children of men exposed to PCDD/Fs for the sampling increased by 25%.

The third generation does not have any deviation from normal distribution on the whole but in both groups a considerable increase of boys born from sons of workers is observed. The deviation is essential at statistical estimation of z-test. Sex ratio values for the city and the total region served as comparison data file (M/M+F=0.51).

We present this fact that may testify to a compensation ability of the population and probably be evidence of more complicated processes connected with the impact of persistent organic pollutants on the reproductive function of male organism. Further monitoring of demographic situation in the cohort may to some extent change but cannot considerably influence the conclusions because the major part of the third generation has been included into calculations as it follows from Figure 1.

Acknowledgements

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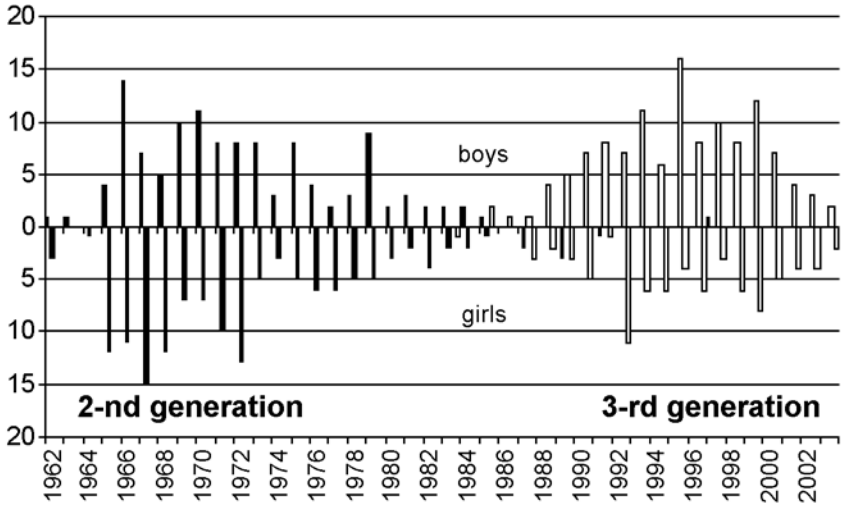

Figure 2. Histogram of sex of 262 children and 218 grandchildren of 193 exposed male workers over time (1962-2004).

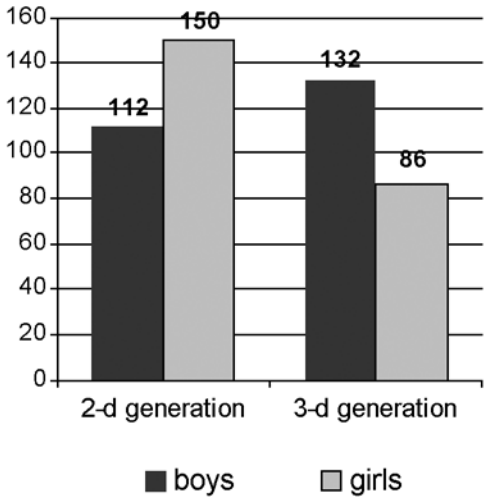

Figure 3. Offspring of exposed male workers (total number), children and grandchildren

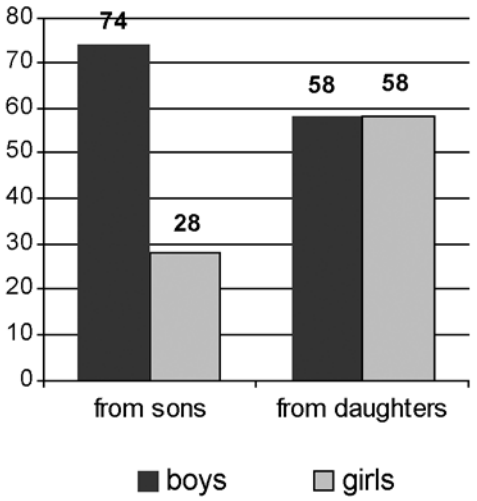

Figure 4. The 3-rd generation, (total number), lines “father-son” and “father-daughter”