doi:10.4149/neo_2009_04_353

Human exposure to polyhalogenated hydrocarbons and incidence of selected malignancies – central European experience

V. BENCKO[1*], J. RAMES[1], M. ONDRUSOVA[2, 3], I. PLESKO[3], L. JURICKOVA[4], T. TRNOVEC[5]

[1]Institute of Hygiene & Epidemiology, First Faculty of Medicine, Charles University in Prague & General University Hospital, Prague, Czech Republic; e-mail: vladimir.bencko@lf1.cuni.cz; [2]National Cancer Registry of the Slovak Republic, National Health Information Center, Bratislava, Slovak Republic; [3]Cancer Research Institute, Slovak Academy of Science, Bratislava, Slovak Republic; [4]Institute of Health Information and Statistics of the Czech Republic, Prague, Czech Republic; [5]National Reference Centre for Dioxins and Related Compounds, Research Base of the Slovak Medical University, Bratislava, Slovak Republic

Received October 10, 2008

This paper describes results of two ecological studies design to analyze the incidence of selected malignancies in two populations exposed to polychlorinated hydrocarbons, mostly PCBs and TCDDs/Fs by comparing data available in the *National Cancer Registry of the Slovak Republic* and *National Oncological Registry of the Czech Republic* databases for the Slovak Republic (~ 5 M inhabitants) and the Czech Republic (10,3 M inhabitants) to the data relevant for the population of Michalovce District, the Slovak Republic (~ 112,000 inhabitants) and Uherske Hradiste, the Czech Republic (146,000 inhabitants). Those districts are recognized as PCB-contaminated areas due to production and industrial use of PCBs.

Data were analyzed for the 10-year period 1987-1996. The age adjusted world standard ratio (WSR) incidence of thyroid, pancreatic, breast, ovarian, bladder, and brain tumors in females and thyroid, pancreatic, breast, bladder, brain, prostate and testicular tumors in males were compared.

Neither PCBs nor TCDDs/Fs appear to contribute to the observed significantly lower incidence of breast and prostate cancer in the Michalovce District and lower bladder cancer incidence in Uherske Hradiste District. However, anti-estrogenic and anti-androgenic properties have been described for hydroxylated and methylsulfonyl PCB metabolites. These properties could contribute to a mechanism through which these metabolites might modulate the development of breast, prostate and bladder cancer.

The results of our analysis points to substantial potential problems of risk assessment for cancer incidence in populations exposed to xenobiotics, or more generally, as it relates to a wide spectrum of confoundings of cancer risk factors.

Key words: polyhalogenated hydrocarbons; anti-estrogenicity; anti-androgenicity; breast cancer; prostate cancer; bladder cancer

Findings regarding the carcinogenicity of polyhalogenated hydrocarbons are inconclusive and even contradictory [1–2].

A population-based cross sectional study (PCB Risk 5th FP) confirmed that the population of the Michalovce District in Eastern Slovakia was exposed to elevated polychlorinated biphenyl (PCB) levels due to the production of 21,500 metric tons of PCBs in a local chemical plant from 1959 – 1983 [3–4]. As such, the Michalovce District is recognized as one of the most heavily PCB-contaminated areas of the world. Due to the inconclusive and at times contradictory findings concerning the carcinogenicity of polyhalogenated hydrocarbons [1-2], this ecological study was conducted to analyze the incidence of selected malignancies in the exposed population by comparing data from the National Cancer Registry of the Slovak Republic database (established in 1975) for the Slovak Republic (~ 5 million inhabitants) and the Michalovce District (~ 112,000 inhabitants). Data were analyzed for the ten-year period 1987-1996 [5].

Increased polyhalogenated hydrocarbons were found in breast milk fat samples collected in the Uherske Hradiste (UH) District compared to that of five other sampled regions throughout the Czech Republic [6–9]. The content of lipophilic xenobiotics corresponded to the values detected in the breast milk samples in Eastern Slovakia, Michalovce District, that were collected according the same protocol within the 5th FP PCBRisk QLK 4-2000-00488 [4]. According to the same protocol, was performed analysis of the same spectrum of malignancies in UH district in comparison with the incidence

* Corresponding author

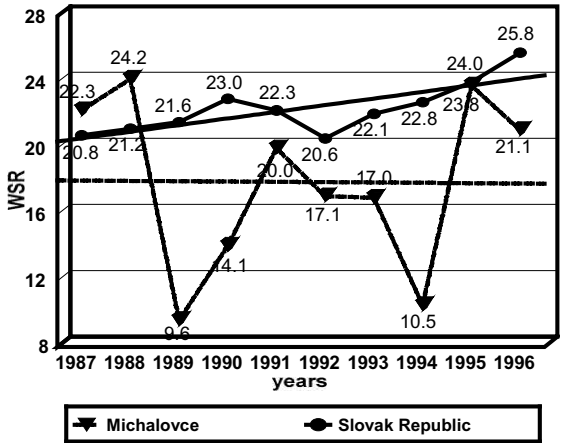

Figure 1. Linear regression of WSR values for prostate cancer in males in the Slovak Republic and Michalovce District.

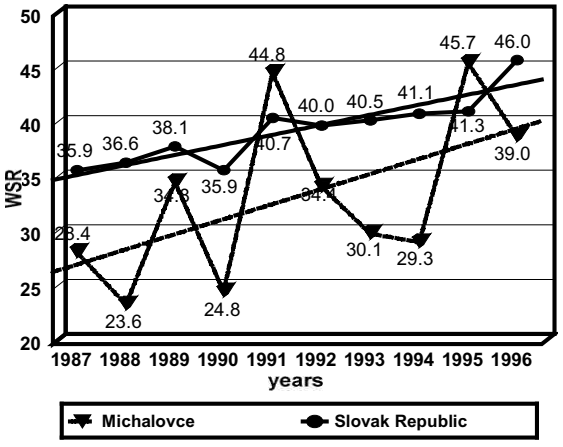

Figure 2. Linear regression of WSR values for breast cancer in females in the Slovak Republic and Michalovce District.

of the malignancies in the Czech Republic for the course in the same time period of ten years (1987-1996). Throughout this ten year period collected dataset for the Czech Republic represents ~103M and for UH District ~1,46 M person years.

Methods

The age-adjusted world standard ratio (WSR) incidence of malignant thyroid, pancreatic, breast, ovarian, bladder, and brain tumors in females and malignant thyroid, pancreatic, breast, bladder, brain, prostate and testicular tumors in males were compared for whole the Slovak Republic and the Michalovce District. For the period 1987-1996, the study base for the Slovak Republic was 50 M person-years and for Michalovce District approximately 1.12 M person-years. Statistical significance was evaluated using two sample paired *t*-tests of the means in the STATISTICA 6.0 software.

Table 1. World standard ratio (WSR) age-adjusted incidence of selected malignancies per 100,000 in males in the exposed district (Michalovce) and the Slovak Republic, during the period 1987 – 1996

	MICHALOVCE		SLOVAK REPUBLIC				
DG	WSR	95% CI	WSR	95% CI	RR	t-test	p-value
C25 PANCREAS	8.78	± 4.38	10.15	± 0.40	0.87	-0.72	0.49
C50 BREAST	0.38	± 0.58	0.46	± 0.09	0.83	-0.32	0.76
C61 PROSTATE	17.97	± 3.76	22.42	± 1.13	0.80	-2.65	0.03
C62 TESTES	6.08	± 2.85	5.44	± 0.58	1.12	0.48	0.65
C67 BLADDER	12.34	± 3.55	14.44	± 0.43	0.85	-1.41	0.19
C71 BRAIN	4.63	± 1.63	5.21	± 0.42	0.89	-0.78	0.45
C73 THYREOID	0.93	± 1.10	1.08	± 0.16	0.86	-0.31	0.77

CI, confidence interval; RR, relative risk of WSR average values for this 10-year period; t-test, t-test value of WSR average values; p-value, p-value in t-test calculation of WSR average values.

Results

The WSR incidence at most cancer sites was not significantly different between the Michalovce District and the whole Slovak Republic. For males, the incidence of prostate cancer was significantly lower in the Michalovce District than in whole the Slovak Republic during the period studied ($p = 0.03$; Table 1 and Figure 1). During this period, the WSR age-adjusted prostate cancer incidence per 100,000 males, resp. females was 22.42 in the Slovak Republic, but only 17.97 in the PCB-contaminated area of Michalovce. For females, the incidence of malignant breast cancer was also significantly lower in Michalovce than in the whole Slovak Republic during the period studied ($p = 0.01$; Table 2; Figure 2). The WSR age-adjusted breast cancer incidence values were 39.61/100,000 and 33.49/100,000 in the Slovak Republic and Michalovce, respectively. This is noteworthy because previous studies have observed that the population in the Michalovce

Table 2. World standard ratio (WSR) age-adjusted incidence of selected malignancies per 100,000 in females in the exposed district (Michalovce) and the Slovak Republic during the period 1987 – 1996

	MICHALOVCE		SLOVAK REPUBLIC				
DG	WSR	95% CI	WSR	95% CI	RR	t-test	p-value
C25 PANCREAS	5.92	± 1.42	5.31	± 0.20	1.11	1.01	0.34
C50 BREAST	33.49	± 5.53	39.61	± 2.22	0.85	-3.11	0.01
C56 OVARIUM	9.73	± 3.04	10.81	± 0.27	0.90	-0.82	0.44
C67 BLADDER	3.29	± 1.14	2.92	± 0.13	1.13	0.70	0.50
C71 BRAIN	4.58	± 1.49	4.06	± 0.31	1.13	0.79	0.45
C73 THYREOID	4.95	± 2.83	3.12	± 0.38	1.59	1.52	0.16

CI, confidence interval; RR, relative risk of WSR average values for this 10-year period; t-test, t-test value of WSR average values; p-value, p-value in t-test calculation of WSR average values.

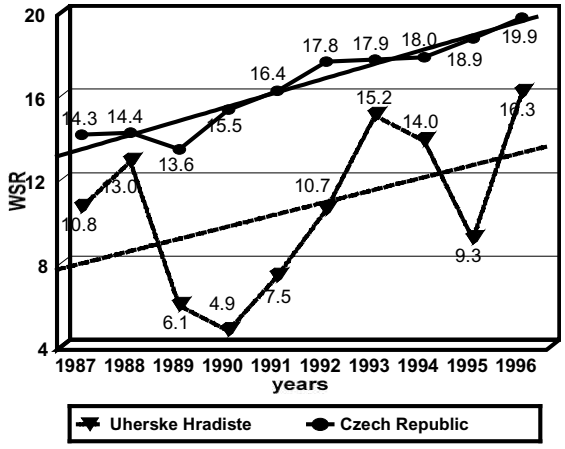

Figure 3. Linear regression of WSR values for bladder cancer in males in Czech Republic and Uherske Hradiste District .

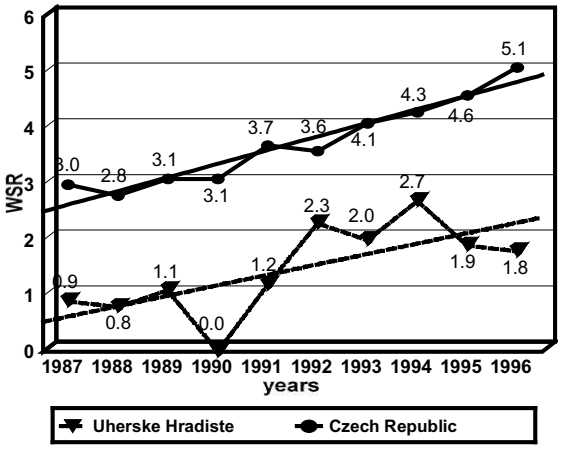

Figure 4. Linear regression of WSR values for bladder cancer in females in Czech Republic and Uherské Hradiště District

District was exposed to higher levels of PCBs than the whole Slovak Republic [3]. The increasing trend in breast cancer in both populations was strikingly similar trough out the follow up period.

The results of age adjusted WSR incidence of selected malignancies in the second study based on database of the National Oncological Registry of the Czech Republic did not offer any striking differences. The only exceptions were malignancies of bladder in both males and females (see table 3 and 4) at the level $p<0.01$. During the follow up period it ranged within 16.67 ± 1.54 per 10^4 in Czech Republic comparing with 10.78 ± 2.77 in Uherske Hradiste District in males and 3.74 ± 0.55 versus 1.47 ± 0.58 per 10^4 in females (see Figs. 3 and 4).

In comparison with previous study in the Slovak Republic in population of the Uherske Hradiste District we found only not statistically significant lower incidence of breast cancer.

Discussion

During recent decades, the possible influence of PCBs on the development of breast cancer has been studied extensively. A few studies reported an association between PCB body burden and a higher incidence of breast cancer [10–12], but the majority of the epidemiological studies did not find an association between PCB exposure and an increased incidence of breast cancer [13–16].

Laboratory studies have demonstrated that PCBs may induce a broad range of estrogenic and anti-estrogenic or androgenic effects [17–24]. A variety of factors including the dose and duration of exposure, and more importantly, the degree of chlorination will influence the nature and severity of effect. Mono-, di-, and tricholrinated biphenyls have very different affinities for biological receptors in comparison to PCBs with six or more chlorines. It is unclear if environmental agents have

Table 3. World standard ratio (WSR) age-adjusted incidence of selected malignancies per 100,000 in males in the exposed district (Uherske Hradiste District) and the Czech Republic, during the period 1987 – 1996

	UHERSKE HRADISTE		CZECH REPUBLIC				
DG	WSR	95% CI	WSR	95% CI	RR	t-test	p-value
C25 PANCREAS	12.18	± 2.22	11.48	± 0.30	1.06	0.65	0.53
C50 BREAST	0.85	± 0.48	0.51	± 0.05	1.67	1.68	0.13
C61 PROSTATE	27.93	± 4.45	26.82	± 3.33	1.04	0.50	0.63
C62 TESTES	5.46	± 1.32	5.48	± 0.42	1.00	-0.04	0.97
C67 BLADDER	10.78	± 2.77	16.67	± 1.54	0.65	-5.77	<0.01
C71 BRAIN	5.66	± 2.24	5.18	± 0.50	1.09	0.53	0.61
C73 THYREOID	2.02	± 0.85	1.34	± 0.16	1.51	1.85	0.10

CI, confidence interval; RR, relative risk of WSR average values for this 10-year period; t-test, t-test value of WSR average values; p-value, p-value in t-test calculation of WSR average values.

Table 4. World standard ratio (WSR) age-adjusted incidence of selected malignancies per 100,000 in females in the exposed district (Uherske Hradiste District) and the Czech Republic, during the period 1987 – 1996

	UHERSKE HRADISTE		CZECH REPUBLIC				
DG	WSR	95% CI	WSR	95% CI	RR	t-test	p-value
C25 PANCREAS	6.43	± 1.74	6.68	± 0.25	0.96	-0.32	0.76
C50 BREAST	44.07	± 7.56	48.67	± 3.34	0.91	-1.39	0.20
C56 OVARIUM	12.56	± 2.95	13.34	± 0.68	0.94	-0.74	0.48
C67 BLADDER	1.47	± 0.58	3.74	± 0.55	0.39	-11.38	<0.01
C71 BRAIN	3.30	± 1.02	3.63	± 0.18	0.91	-0.83	0.43
C73 THYREOID	3.90	± 2.03	3.52	± 0.47	1.11	0.42	0.68

CI, confidence interval; RR, relative risk of WSR average values for this 10-year period; t-test, t-test value of WSR average values; p-value, p-value in t-test calculation of WSR average values.

contributed to the lower incidence of breast or prostate cancer observed in the Michalovce district. The anti-estrogenic properties of hydroxylated and methylsulfonyl PCB metabolites may help explain the lower incidence of breast cancer in the Michalovce District as well as the observed lower incidence of bladder malignancies in Uherské Hradiste District.

In conclusion the results of our descriptive study point to substantial potential problems of risk assessment for cancer incidence in populations exposed to xenobiotics, or more generally, as it relates to a wide spectrum of confoundings of cancer risk factors.

Acknowledgements. This study was supported by the 5th FP Project Evaluating Human Health Risk from Low-dose and Long-term PCB Exposure (PCBRISK) QLK4-2000-00488, and in a statistical analysis phase by the League Against Cancer Prague, grant No. 200/02/289 and by CASCADE Network of Excellence in the 6th FP EC.

References

[1] Bencko V. Risk assessment and human exposure to endocrine disrupters. In: Jedrychowski W.A., Perera F.P., Maugeri U. (eds) Molecular Epidemiology in Preventive Medicine, International Center for Studies and Research in Biomedicine in Luxembourg 2003; 315–27.

[2] Pavuk M, Cerhan JR, Lynch CF et al. Environmental exposure to PCBs and cancer incidence in eastern Slovakia. Chemosphere 2004; 54: 1509–20. doi:10.1016/j.chemosphere.2003.10.038

[3] Kocan A, Petrik J, Jursa S et al. Environmental contamination with polychlorinated biphenyls in the area of their former manufacture in Slovakia. Chemosphere 2001; 43: 595–600. doi:10.1016/S0045-6535(00)00411-2

[4] Trnovec T, Bencko V, Langer P et al. PCBRISK Project Slovakia: Study design, objectives, hypotheses, main findings, health consequences for the population exposed, rationale of future research, Dioxins 2004, Berlin. Organohalogen Compounds 2004; 66: 3573–3579.

[5] Bencko V, Rames J, van den Berg M et al. Human exposure to polyhalogenated hydrocarbons and incidence of selected malignancies. In: Donnelly and Leslie H Cizmas (eds) Environmental Health in Central and Eastern Europe. Dordrechr: Springer 2006; 31–37.

[6] WHO/ECEH (1996) Levels of PCBs, PCDDs and PCDFs in Human Milk. Second Round of WHO co-ordinated Exposure Study. Environmental Health in Europe Series 1996; 3: 121.

[7] Bencko V, Skulova Z, Krecmerova M et al. Selected polyhalogenated hydrocarbons in breast milk. Toxicol Lett 1998; 96–97: 341–345. doi:10.1016/S0378-4274(98)00091-5

[8] Bencko V, Cerna M, Jech L et al. Exposure of breast-fed children in the Czech Republic to PCDDs, PCDFs, and dioxin-like PCBs. Environmental Toxicology and Pharmacology 2004; 18: 83–90. doi:10.1016/j.etap.2004.01.009

[9] Cerna M, Bencko V. Polyhalogenated hydrocarbons in human samples of the Czech and Slovak populations: A review I. Polychlorinated biphenyls. Centr Eur J Publ Health 1999; 7: 67–71.

[10] Aronson KJ, Miller AB, Woolcott CG et al. Breast adipose tissue concentrations of polychlorinated biphenyls and other organochlorines and breast cancer risk. Cancer Epidemiol Biomarkers Prev 2000; 9: 55–63.

[11] Guttes S, Failing K, Neumann K et al. Chlororganic pesticides and polychlorinated biphenyls in breast tissue of women with benign and malignant breast disease. Arch. Environ. Contam Toxicol 1998; 35: 140–7. doi:10.1007/s002449900361

[12] Lucena RA, Allam MF, Costabeber IH et al. Breast cancer risk factors: PCB congeners. Eur J Cancer Prev 2001; 10: 117–9. doi:10.1097/00008469-200102000-00018

[13] Helzlsouer KJ, Alberg AJ, Huang HY et al. Serum concentrations of organochlorine compounds and the subsequent development of breast cancer. Cancer Epidemiol Biomarkers Prev 1999; 8: 525–32.

[14] Laden F, Ishibe N, Hankinson SE et al. Polychlorinated biphenyls, cytochrome P450 1A1 and breast cancer risk in the Nurses' Health Study. Cancer Epidemiol Biomarkers Prev 2002; 11: 1560–5.

[15] Wolff MS, Zeleniuch-Jacquotte A, Dubin N et al. Risk of breast cancer and organochlorine exposure. Cancer Epidemiol Biomarkers Prev 2000; 9: 271–7.

[16] Zheng T, Holford TR, Tessari J et al. Breast cancer risk associated with congeners of polychlorinated biphenyls. Am J Epidemiol 2000; 152: 50–8. doi:10.1093/aje/152.1.50

[17] Safe SH. Polychlorinated biphenyls (PCBs): Environmental impact, biochemical and toxic responses, and implications for risk assessment. Crit Rev Toxicol 1994; 24: 87–149. doi:10.3109/10408449409049308

[18] Safe S, Wang F, Porter W et al. Ah receptor agonists as endocrine disruptors: antiestrogenic activity and mechanisms. Crit Rev Toxicol 1998; 102–103: 343–7.

[19] Safe S, Wormke M et al. Mechanisms of inhibitory aryl hydrocarbon receptor-estrogen receptor crosstalk in human breast cancer cells. J Mammary Gland Biol Neoplasia 2000; 5: 295–306. doi:10.1023/A:1009550912337

[20] van den Berg M, Birnbaum L, Bosveld BTC et al. Toxic equivalency factors (TEFs) for PCBs, PCDDs and PCDFs for humans and wildlife. Environ Health Perspect 1998; 106: 775–792. doi:10.2307/3434121 PMid:9831538 PMCid:1533232

[21] Moore M, Mustain M, Daniel K et al. Antiestrogenic activity of hydroxylated polychlorinated biphenyl congeners identified in human serum. Toxicol Appl Pharmacol 1997; 42: 160–8. doi:10.1006/taap.1996.8022

[22] Letcher RJ, Lemmen JG, van der Burg B et al. In vitro antiestrogenic effects of aryl methyl sulfone metabolites of polychlorinated biphenyls and 2,2-bis(4-chlorophenyl)-1,1--dichloroethene on 17beta-estradiol-induced gene expression in several bioassay systems. Toxicol Sci 2002; 69: 362–72. doi:10.1093/toxsci/69.2.362

[23] Cantón RF, Sanderson LT, Bergman et al. [Abstract]. Effects of brominated flame retardants on activity of the steroidogenic enzyme aromatase (CYP19) in H295R human adrenocortical carcinoma cells in culture. Presented at the Dioxin conference, (Boston 2003).

[24] Sasco AJ. Cancer and globalization. Biomed Pharmacother 2007; 62: 110–121. doi:10.1016/j.biopha.2007.10.015