WASABY

WAter and Soil contamination and Awareness on Breast cancer risk in Young women

# D7.1 ANNEXES 1-8

## Literature review on the main persistent environmental contaminants related to breast cancer

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## ANNEX 1 – 8 (Legend)

The results of the research of the 130 scientific articles are summarized in eight annexes in the form of tables for the different classes of persistent contaminants.

All the schematic tables have the same approach, starting from the name of the first three researchers of the scientific journal, what kind of design of the observational study (case-control, cohort, etc.) and the place, exposure to the main persistent contaminants, the years of interest of the study, the relative risk, the main comments relevant to the scientific article and the possible covariates and methods used.

The lines highlighted in green, are the scientific articles, which found a statistically significant risk of the three persistent contaminants considered in relation with breast cancer, we also took into account the articles where even one congener of persistent contaminant (eg PCB-203) and the significant relationship with the breast cancer.
Blanks are all articles where there is no statistically significant relationship between the persistent contaminant and the breast cancer.

Forward, we have included, in the ANNEX (1-8), the principal Monographs IARC for the classes of persistent pollutants analyzed, the main reviews and meta - analyzes always between the correlation of the persistent contaminants and the breast cancer.

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## ANNEX 1 – References PCBs articles

| N° | Name of researchers / scientific journal | Place and study design | Exposure contaminants | Exposure assessment procedure | Time of sample collecting | Years of the Study interest | Exposure category or level / Risk estimate (95% CI) | Relevant Comment | Methods and possible covariates |
|---|---|---|---|---|---|---|---|---|---|
| 1 | **Gammon MD**, Wolff MS, et al. Vol. 11, 686–697, **Cancer Epidemiology, Biomarkers & Prevention; 2002;** | Case-control study. Long Island, NY. **USA** | PCBs, DDE, Chlordane, Dieldrin. | Blood Samples | After diagnosis | 1996-1997 | No substantial elevation in breast cancer risk was observed in relation to the highest quintile of lipid-adjusted serum levels of PCBs | No statistically significant results for other contaminants measured. | Age, race, reproductive history, benign breast disease Interview response rates: cases, controls, |
| 2 | **Hoyer AP**, Jorgensen T, Rank F, et al. **BMC Cancer. 1:8. 2001.** | Nested case-control study. **Danish** | Total PCB; Dieldrin, HCB. | Blood Samples | Before diagnosis | 1976 - 1978 | Overall breast cancer survival in relation to serum concentrations of organochlorines by estrogen receptor status. Estrogen receptor positive ΣPCB: OR = 2.5 (1.1-5.7) | The results do not suggest that exposure to potential estrogenic organochlorines leads to development of an ERP breast cancer. | Breast cancer characteristics included tumor size, degree of spread, and stage of disease. |
| 3 | **Krieger N**, Wolff MS, Hiatt RA, et al. **Journal of the National Cancer Institute, Vol 86, No. 8, April 20. 1994.** | Nested case-control study; San Francisco Bay Area, **USA** | PCBs, DDE, DDT. | Serum | After diagnosis or at most 6 months before | 1964 – 1990 | Matched analyses found no differences in the case patients' and control subjects' serum levels of DDE or PCBs. | Conclusion: The data do not support the hypothesis that exposure to DDE and PCBs increases risk of breast cancer. | Race, age, date of entry, duration of follow up, BMI, age at menarche, menopausal status, ever pregnant No. and list of PCB congeners not provided. |
| 4 | **Falck FJ**, Ricci A Jr, Wolff MS, et al. **Arch Environ Health 47:143-146.1992.** | Case-control study; **Connecticut** | PCBs, DDT, DDE, HCB, HCH. | Adipose breast tissue | After diagnosis | 1987-1992 | The study by Frank Falck et al., showing higher chlorinated PCBs among 20 breast cancer cases, compared with 20 women with benign breast disease | There was approximately 1% increased risk for every 10 ppb of DDE and PCBs in adipose tissue. | The association persisted after controlling for age, smoking, and BMI. |
| 5 | **Rubin CH**, Lanier A, Kieszak S, et al. **International journal of circumpolar health** 65(1):18–27. **2006.** | Case-control study; **Alaska** | PCBs, DDT, DDE. | Serum Samples | Before diagnosis | 1983-1987 | OR = 1.43 (0.46, 4.47) for the highest tertile of DDE exposure and OR = 0.42 (0.07, 2.38) for the highest tertile of total PCB exposure. | Our results confirm exposure to organochlorines among Alaska. Native women but do not identify these exposures as a significant risk factor for breast cancer. | Parity, family history of breast cancer, race, triglycerides, cholesterol. |

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| N° | Name of researchers / scientific journal | Place and study design | Exposure contaminants | Exposure assessment procedure | Time of sample collecting | Years of the Study interest | Exposure category or level / Risk estimate (95% CI) | Relevant Comment | Methods and possible covariates |
|---|---|---|---|---|---|---|---|---|---|
| 6 | **Recio-Vega R**, Velazco-Rodriguez V, Ocampo-Gómez G, et al. **J Appl Toxicol, 31(3):270-8**. **2011.** | Case-control study. Comarca Lagunera, **Mexico**. | PCBs | Blood Samples | After diagnosis | 2000-2007 | They found 8 congeners PCBs (118, 128, 138, 170, 180, 195, 206 and 209) positively associated with BC risk. | statistically significant positive association between 8 congeners PCBs and BC risk | Age, age at menarche, lactation, menopausal status, BMI. |
| 7 | **Cohn BA**, Terry MB, Plumb M, et al. **Breast Cancer Res Treat 136(1):267–275. 2012.** | Prospective case-control study. Oakland, **California** | PCBs | Postpartum SERUM samples | Before diagnosis | 1959 - 1998 | Estimated net effects of PCB exposure on risk of breast cancer before 50 years of age. In contrast, PCB 203 was associated with a six fold increased risk (OR, 75th vs. 25th percentile = 6.3, 95 % CI 1.9, 21.7). | statistically significant positive association for PCB 203 | Age, cholesterol, triglycerides, race, parity, lactation, BMI, year of blood collection. |
| 8 | **Arrebola JP**, Belhassen H, Artacho-Cordón F, et al. **Sci Total Environ 520: 106–113. 2015.** | Case–control study. **Tunisia** | PCB 138, PCB 153, PCB 180 | Serum Samples | After diagnosis | 2012 | Concentrations of PCB 138, PCB 180, were significantly or borderline significantly higher in cases than in controls. | statistically significant positive association for PCB 138, 180. | Age, BMI, occupational class, residence, education, accumulated lactation time, parity, menopausal status, family history of breast cancer, total serum lipid |
| 9 | **Gatto NM**, Longnecker MP, Press MF, et al. Cancer Causes Control.18:29–39. **2007.** | Case–control study **USA** | PCBs, DDE, DDT. | Blood Samples | After diagnosis | 1995-1998 | PCBs: OR = 1.01, 95% CI = (0.63,1.63) | Breast cancer risk was not associated with increasing quintiles of lipid-adjusted PCBs or DDE | Age, BMI, lactation, lipid. |
| 10 | **Wolff MS**, Zeleniuch-Jacquotte A, et al. **Cancer Epidemiology Biomarkers Prev**, 9(3):271–7. **2000** | nested case-control study New York, **USA** | PCBs, DDE. | Serum Samples | 6 months or more before breast cancer diagnosis | 1994 - 1996 | Quartiles of PCB concentration (ng/g lipid)<br>478–638<br>OR=1.55 (0.59–4.12)<br>639–876<br>OR=1.23 (0.49–5.08)<br>> 876<br>OR=2.02 (0.76–5.37)<br>P for trend = 0.23 | Association not statistically significant | Age, menopausal status, date of blood collection (matching), age at menarche, number of pregnancies, age at first pregnancy, family history of breast cancer, lactation, height. |

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| N° | Name of researchers / scientific journal | Place and study design | Exposure contaminants | Exposure assessment procedure | Time of sample collecting | Years of the Study interest | Exposure category or level / Risk estimate (95% CI) | Relevant Comment | Methods and possible covariates |
|---|---|---|---|---|---|---|---|---|---|
| 11 | **Itoh H**, Iwasaki M, Hanaoka T, et al. **Cancer Causes Control, 20(5):567–80. 2009.** | Case–control hospital study **Japan** | PCBs, DDT. | Serum Samples | After diagnosis | 2001 - 2005 | PCB-153 NR 0.40 (0.18–0.91) P for trend = 0.04<br>PCB-138 NR 0.61 (0.28–1.35) P for trend = 0.29<br>PCB-180 NR 0.29 (0.13–0.66) P for trend = 0.004 | No association was identified between PCBs and risk of breast cancer | Age, total lipid concentration in serum, BMI, reproductive risk factors, medical history, area, lipid, menopause, smoking, fish and vegetable consumption, family history of breast cancer, age at first child birth, age at menarche, history of breast cancer screening, lactation. |
| 12 | **Zheng T**, Holford TR, Tessari J, et al. **Am J Epidemiol, 152(1):50–8. (2000a).** | Case–control study. Connecticut, **USA.** | PCBs | Serum Samples and adipose tissue | After diagnosis | 1994–1997 | PCBs (ppb) 396.0–562.9 79 exposed cases 0.6 (0.4–1.0) (ppb) ≥ 563.0 114 exposed cases 0.7 (0.4–1.1) | No association was identified between PCBs and risk of breast cancer | Age, BMI, structured interview; lipid-adjusted breast adipose tissue concentrations of 9 PCB congeners measured by GC (ng/g lipid) |
| 13 | **Zheng T**, Holford TR, Mayne ST, et al. **Cancer Epidemiol Biomarkers Prev, 9(2):167–74. (2000b).** | Case–control study. Connecticut, **USA.** | PCBs | Serum Samples and adipose tissue | After diagnosis | 1995–1997 | Total PCBs (ppb) 604.1–800.0 160 exposed cases 1.04 (0.76–1.45)<br>(ppb) > 800.0 160 exposed cases 0.95 (0.68–1.32)<br>P for trend = 0.41 | NEGATIVE No association was identified between PCBs and risk of breast cancer | Age, BMI, structured interview; lipid- adjusted serum concentrations of 9 PCB congenerers measured by GC (ng/g lipid) |
| 14 | **Demers A,** Ayotte P, Brisson J, et al. **Cancer Epidemiol Biomarkers Prev, 9(2):161–6. 2000.** | Case–control study. Quebec City, **Canada.** | PCBs, DDE. | Serum Samples | After diagnosis | 1994–1997 | PCB-153 (µg/kg, lipid basis) 36.3–46.6, Hospital OR (95% CI)1.02 (0.54–1.94) Population OR (95% CI) 1.12 (0.66–1.88)<br>46.6–57.1, Hospital OR (95% CI) 0.99 (0.50–1.93)<br>Population OR (95% CI) 0.94 (0.55–1.62) | Women diagnosed with breast cancer who had higher plasma concentrations of p,p'-DDE, b-HCH, oxychlordane, or trans-nonachlor were more likely to show both a large tumor (diameter > 2 cm) and axillary-lymph-node involvement. | Age, BMI, alcohol consumption, age at first cigarette, number of fertile years, age at first child, total breast feeding duration, use of oral contraceptive, use of hormone therapy, first-degree family history of breast cancer, history of benign breast disease, and time separating blood sampling from surgery. |

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| N° | Name of researchers / scientific journal | Place and study design | Exposure contaminants | Exposure assessment procedure | Time of sample collecting | Years of the Study interest | Exposure category or level / Risk estimate (95% CI) | Relevant Comment | Methods and possible covariates |
|---|---|---|---|---|---|---|---|---|---|
| 15 | **Demers A**, Ayotte P, Brisson J, et al. **Am J Epidemiol, 155(7):629–35. 2002.** | Case–control study. Quebec City. **Canada.** | PCBs | Serum Samples | After diagnosis | 1994–1997 | PCB 105, 118, and 156 expressed as 2,3,7,8-tetrachlorodibenzo-p-dioxin toxic equivalents OR = 2.02, 95% CI: 1.24, 3.28; fourth vs. first quartile | There is a statistically significant association for PCB 105, 118, and 156 expressed as 2,3,7,8-tetrachloro dibenzo-p-dioxin toxic | Information on age, BMI, lifestyle, dietary habits, and reproductive history was obtained by telephone interview. |
| 16 | **Holford TR**, Zheng T, Mayne ST, et al. **Int J Epidemiol. Dec; 29(6):975-82. 2000.** | Case–control study. Connecticut. **USA.** | nine PCB congeners (74, 118, 138, 153, 156, 170, 180, 183, 187) | Breast adipose tissue samples | After diagnosis | 1994–1997 | Linear logistic model 10-ppb change in exposure PCB-183 OR=1.82 (95% CI; 1.12–2.98) | PCB-183 were associated with increased risk of cancer of the breast. | Age, BMI, reproductive risk factors, dietary fat intake, income, fat concentrations of PCB |
| 17 | **Zhang Y**, Wise JP, Holford TR, et al. **Am J Epidemiol, 160(12):1177–83. 2004.** | Case–control study. Connecticut. **USA** | PCBs | Serum Samples | After diagnosis | 1999–2002 | No significant association for CYP1A1 m1 or m4 genotype or in premenopausal women. | The CYP1A1 m2 genetic polymorphism was associated with increased risk of female breast cancer and may modify the relation between PCB exposure and breast cancer risk. | Age, BMI, lipid-adjusted serum concentrations of 9 PCB congeners. Genotyping of CYP1A1 m1, m2, and m4 by PCR-RFLP |
| 18 | **Rusiecki JA**, Holford TR, Zahm SH, et al. **Eur J Epidemiol, 19(8):793–801. 2004.** | Case–control study. Connecticut. **USA** | PCBs | Blood serum and Adipose tissue samples | After diagnosis | 1994–1997 | Tumours were apparent with concentrations of PCB-183 (third tertile vs first: OR, 2.4; 95% CI, 1.0–6.0, P for trend = 0.03, but data not otherwise shown). | Analyses for individual congeners did not show any association | Age, reproductive risk factors, BMI, family history of breast cancer in a first-degree relative. |
| 19 | **Laden F**, Hankinson SE, Wolff MS, et al. **Int J Cancer.** 91(4):568–74. **2001.** | nested case-control study **USA** | PCB and DDE | Plasma | After and before diagnosis | 1976–1994 | OR for breast cancer associated with PCBs was 0.94 (95% CI 0.73 to 1.21), and the equivalent OR for breast cancer associated with DDE was 0.99 (95% CI 0.77 to 1.27). | no significant associations were found between organochlorine levels in serum and breast cancer risk. | Age, family history of breast cancer, history of BBD, age at menarche, BMI, lipid, number of children, age at birth of first child, lactation. |
| 20 | **Ward EM**, Schulte P, Grajewski B, et al. **Cancer Epidemiol Biomarkers Prev. 9(12):1357-67. 2000.** | (nested case-control study **Norway** | PCBs | Serum | before diagnosis | 1973 - 1991 | The current study did not find any evidence for an association between organochlorine levels in serum and breast cancer. | no significant associations were found between organochlorine levels in serum and breast cancer risk. | Age, BMI, occupational category, lipid concentration in serum, year blood collected, age at blood collection. Age at first birth |

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| N° | Name of researchers / scientific journal | Place and study design | Exposure contaminants | Exposure assessment procedure | Time of sample collecting | Years of the Study interest | Exposure category or level / Risk estimate (95% CI) | Relevant Comment | Methods and possible covariates |
|---|---|---|---|---|---|---|---|---|---|
| 21 | **Helzlsouer KJ,** Alberg AJ, Huang H-Y, et al. **Cancer Epidemiol Biomarkers Prev. 8(6):525–32. 1999.** | nested case-control study **USA** | PCBs, DDE, DDT. | Serum | before diagnosis | 1974 - 1994 | The risk of developing breast cancer also tended to decrease with increasing levels of PCBs. | no significant associations were found between organochlorine levels in serum and breast cancer risk. | Adjustment for family history of breast cancer, BMI, age at menarche or first birth, and months of lactation, lipid concentration in serum. |
| 22 | **Dorgan JF,** Brock JW, Rothman N, et al. Cancer Causes Control.10(1):1–11. **1999.** | nested case-control study **USA** | PCBs and DDT. | Blood Sample | before diagnosis | 1977 - 1987 | Women with higher serum levels of other organochlorine pesticides and PCBs showed no increased risk of breast cancer. | Results of this study do not support a role for organochlorine pesticides and PCBs in breast cancer etiology. | Age, BMI, menopausal status, family history, estrogen use, parity, age at menarche |
| 23 | **Hoyer AP,** Grandjean P, Jørgensen T, et al.. **The Lancet. 352(9143):1816–20.1998.** | nested case-control study. **Denmark** | PCBs, Dieldrin, DDT. | Serum | After diagnosis | 1976 – 1995 | PCB<br>OR= 1.11;<br>(95% CI 0.70–1.77)<br>Association not statistically significant with breast cancer | No association statistically significant was identified between PCBs, Dieldrin, DDT and risk of breast cancer | Age, weight, height, number of children, alcohol, smoking, lipid, physical activity, menopausal status, household income, marital status, education. |
| 24 | **Raaschou-Nielsen O,** Pavuk M, LeBlanc A, et al. **Cancer Epidemiol Biomarkers Prev. 14(1):67–74. 2005.** | nested case-control study **Denmark** | PCBs and others organochlorine compound. | Adipose breast tissue | Tissue was sampled up to 6.5 years before the breast cancer diagnosis | 1993 – 1997 | The results showed no higher risk of breast cancer among women with higher levels of any pesticides or polychlorinated biphenyls; | No association statistically significant was identified between PCBs and others organochlorine compound and risk of breast cancer | Age, education, BMI, lipid, alcohol, number of children, age at birth of first child, lactation, HRT, history of BBD. |
| 25 | **Zhang H**, Liu L, Zhang P, et al. **Journal of hygiene research. 42(1):44–8. 2013.** | case-control study **China** | PCB 28 and PCB 52, HCH, DDE. | Serum | / | 2010 – 2011 | PCBs<br>OR= 7.46;<br>95% CI 2.44– 22.81 | Organochlorines resides, including DDT, HCH and PCB, may increase women's risk of getting breast cancer. | Age, family history of breast cancer, history of BBD, age at menarche, lactation, menstrual cycle, time between menarche and prim parity, bean products intake. |
| 26 | **Charlier C,** Pitance F, Plomteux G. **Bull Environ Contam Toxicol, 71(5):887–91**. **2003.** | case-control study **Belgium** | PCBs | Serum | After diagnosis | NR | PCB-101 and PCB-153 were significantly higher for cases than controls. | Further results are necessary | Age, age at menarche, menopause, HRT, parity, lactation, family history of breast cancer. |

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|---|---|---|---|---|---|---|---|---|---|
| 27 | **Charlier CJ,** Albert AI, Zhang L et al. **Clin Chim Acta. 347(1):177–81. 2004.** | case-control study **Belgium** | PCBs | Serum | After diagnosis | NR | PCB153 (ppb) OR = 1.8 (95% CI1.4– 2.5) < 0.0001 | These results suggest that environmental exposure to PCBs may contribute to multifactorial pathogenesis of breast cancer. | Age, age at menarche, menopause, HRT, parity, lactation, family history of breast cancer. |
| 28 | **Lopez-Carrillo L,** Lopez-Cervantes M, Torres-Sanchez L et al. **Eur J Cancer Prev. 11(2):129–35. 2002.** | case-control study **Mexico** | PCBs , HCH, HCB. | Serum | Before and after diagnosis | 1994 - 1996 | OR 1.31; 95% CI 0.33, 5.21 | This study lends no support to the case for a role for b-HCH, HCB or PCBs in breast cancer aetiology. | Age at menarche, number of children, age at first birth, lactation, lipid, family history of breast cancer, menopausal status, quetelet index. |
| 29 | **Moysich KB,** Ambrosone CB, Vena JE, et al. **Cancer Epidemiol Biomarkers Prev. 7(3):181–8. 1998.** | case-control study **USA** | PCBs, DDE, HCB. | Serum | After diagnosis | 1986 - 1991 | PCBs OR=1.66; 95% CI,1.07–2.88 for the combined second and third tertiles); association with total PCBs OR= 2.87; 95% CI, 1.01–7.29) and moderately chlorinated PCBs OR=3.57; 95% CI,1.10–8.60. | These results suggest that an increase in risk of postmenopausal breast cancer associated with environmental exposure to PCBs | Age, education, family history of breast cancer, parity, quetelet index, lactation, age at first birth, years since last pregnancy, fruit and vegetable intake, lipid. |
| 30 | **Millikan R,** DeVoto E, Duell EJ et al. **Cancer Epidemiol Biomarkers Prev. 9(11):1233–40. 2000.** | case-control study **USA** | PCBs, DDE | Plasma | After diagnosis | 1993 – 1996 | PCB exposure among African-American women (third tertile) OR=1.74; 95% CI,1.00–3.01) African-Americans with BMI > 34.2 (third tertile total PCBs, OR= 4.92; 95% CI,1.63–14.83 | We observed no overall association between plasma levels of DDE and total PCBs but for breast cancer among African-American there is an association | Age, age-squared, race (all participants), lipid, menopausal status, BMI, parity / lactation, HRT, income. |
| 31 | **Stellman SD,** Djordjevic MV, Britton JA, et al. **Cancer Epidemiol Biomarkers Prev. 9(11):1241–9. 2000.** | case-control study **USA** | PCBs | Adipose tissue | After diagnosis | 1994 – 1996 | PCB 183 Concentration in adipose tissue (ng/g) OR 2.00; 95% CI (1.20 – 3.40). | Only PCB congener 183 is significantly associated with risk, with an adjusted odds ratio of 2.0 (95% confidence interval, 1.2–3.4) in women with adipose levels >5.67 ng/g; | Age, BMI, lipid, hospital, race. |

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| N° | Name of researchers / scientific journal | Place and study design | Exposure contaminants | Exposure assessment procedure | Time of sample collecting | Years of the Study interest | Exposure category or level / Risk estimate (95% CI) | Relevant Comment | Methods and possible covariates |
|---|---|---|---|---|---|---|---|---|---|
| 32 | **Aronson KJ,** Miller AB, Woolcott CG, et al. **Cancer Epidemiol Biomarkers Prev.9(1):55–63. 2000.** | case-control study **Canada** | Breast adipose tissue concentrations of polychlorinated biphenyls and other organochlorines and breast cancer risk. | Adipose tissue | Before diagnosis | 1995 – 1997 | *Aroclor 1260 OR 1.15; 95% CI (0.58–2.25). *Total PCBs was calculated as the sum of PCBs 138 and 153 multiplied by 5.2 to approximate a level of the commercial PCB mixture, Alaclor 1260. PCB 105 = OR 3.17; 95% CI (1.51–6.68). PCB 118 = OR 2.31; 95% CI (1.11–4.76). | This study demonstrates increased breast cancer risk associated with the breast adipose tissue concentrations of some specific PCB congeners, but inconsistent or null results for the other compounds that were measured. | Age, BMI, race, lipid, family history, fat intake, alcohol. |
| 33 | **Muscat JE,** Britton JA, Djordjevic MV, et al. **Cancer Epidemiol Biomarkers Prev. 12(12):1474-8. 2003.** | hospital-based case-control study Long Island, New York . **USA** | PCBs, p,p -DDE, trans-nonachlor, oxychlordane, -hexachlorocyclohexane and hexachlorobenzene. | Adipose tissue | After diagnosis | 1994 – 1996 | RR of breast cancer recurrence associated with adipose concentrations of PCBs Total PCB Highest tertile OR 2.9; 95% CI (1.02–8.2) PCB 118 Highest tertile OR 4.0; 95% CI (1.32–4.9) PCB 118 Highest tertile OR 2.6; 95% CI (1.0–7.1 ) PCB 167 Highest tertile OR 3.1; 95% CI (1.0–9.3) | In summary, these results suggest that relatively high PCBs concentrations were related to increased rate of breast cancer recurrence, although this contrasts with our previous data showing no effect of OCs on breast cancer risk in these women. | Age, BMI, and stage of disease at diagnosis, spearman correlation coefficients were calculated to determine the associations between log OC concentrations and |
| 34 | **Wielsoe M,** Kern P, Bonefeld-Jørgensen EC. **Environmental Health 16:56, 2017;** | Case-control study of Inuit women from **Greenland** | Serum levels of environmental pollutants is a risk factor for breast cancer in Inuit: a case control study. | Serum | After diagnosis | 2000-2003 and 2011-2014 | Odds ratio of breast cancer risk associated with serum levels of PCB Grp2 (µg/Kg lipid) ΣPCB Grp2 (OR (95% CI)) 1.00 (reference) 2nd Tertile 2.28 (1.01; 5.18) 3rd Tertile 2.14 (0.94; 4.88) | Significant, positive associations between breast cancer risk and PCBs and PFAAs were observed. The associations indicate that environmental exposure to POPs can be a factor increasing the risk for breast cancer in Inuit women. | Information about age, BMI, smoking status, menopause status, number of full term pregnancies, and history of breastfeeding was obtained from questionnaires. |

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| N° | Name of researchers / scientific journal | Place and study design | Exposure contaminants | Exposure assessment procedure | Time of sample collecting | Years of the Study interest | Exposure category or level / Risk estimate (95% CI) | Relevant Comment | Methods and possible covariates |
|---|---|---|---|---|---|---|---|---|---|
| 35 | **Holmes AK,** Koller KR et al. **International Journal of Circumpolar Health 73, 257-60. 2014;** | case-control study. Alaska **USA** | concentrations of polychlorinated biphenyls and other organochlorines and breast cancer risk. | Blood serum and Adipose tissue samples | After diagnosis | 1999 - 2002 | Persistent pesticides, PCBs, and most phthalate metabolites were not associated with case status in univariate logistic regression. | Our study is limited by small sample size and an inability to control for the confounding effects of body mass index. | Age, BMI, family history, lactation, menopausal status, hormone use, number of live birth. |
| 36 | **Liljegren G,** Hardell L, Lindström G, Dahl P, Magnuson A. **Eur J Cancer Prev. 1998.** | Case-control study. **Sweden** | PCBs, DDE, HCB. | Adipose tissue | After diagnosis | 1993–1995 | PCB, pg/g lipid PCB #77 > 4.5 pg/g lipid (OR = 5.8, 95% confidence interval (CI) = 0.8-42), PCB #126 > 145 pg/g lipid (OR = 2.2, 95% CI = 0.2-18), PCB #169 > 90 pg/g lipid (OR = 7.8, 95% CI = 0.6-96), and for HCB > 40 ng/g lipid (OR = 1.9, 95% CI = 0.4-7.2) | No significant difference for the sum of non co-planar PCBs or DDE was found between cases and controls. | Age, family history, menopausal status, |
| 37 | **Lucena RA**, Allam MF et al. Eur. J. Cancer Prev. 10, 117–119. **2001;** | Case-control study. **Spain** | Breast cancer risk factors: PCB congeners. | Adipose tissue | After diagnosis | 1997 | The most important risk factor identified by the model was PCB n-28 OR 9.6 (95% CI = 3.8 - 24.4) | The magnitude of association between PCB n-28 and breast cancer OR 9.6. together with the fact that its exposure proceeded the effect show the internal validity. | Age, family history, lactation, smoking habitat |
| 38 | **Hoyer AP,** Jørgensen T, Grandjean P, Hartvig HB. **Cancer Causes Control, 11(2):177–84. 2000;** | Copenhagen City Heart Study (CCHS). **Denmark** | Breast cancer risk factors: PCB congeners. | Serum | After diagnosis | 1976 - 1983 | A statistically significant increased risk and trend was found for subjects in the highest quartile of PCB-138 concentration (average of two measurements; OR, 2.1; 95% CI, 1.0–4.4; P for trend = 0.04). Elevated odds ratios were reported for the highest quartile of exposure to total PCBs and congeners PCB-118 and PCB-153 (OR, 1.6, 1.9 and 1.3, respectively | This study provides new evidence of the adverse effect of some organochlorines on breast cancer risk. Furthermore, repeated assessment of exposure during a relevant time period may provide a more precise risk estimate than a single measurement. | Age, BMI, height, number of full-term pregnancies, alcohol consumption, smoking, physical activity, menopausal status, household income, marital status, and education. |

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## ANNEX 1 – References PCBs monographs IARC, reviews, meta – analysis.

| N° | Monographs IARC - PCBs | N° | Reviews - PCBs |
|---|---|---|---|
| 1 | **IARC Monographs PCB N° 107 - Lyon 2016** | 1 | **Mouly TA,** Toms LML. Environ Sci Pollut Res.Volume 23, Issue 22, pp 22385–22407. **2016.** |
| | **Meta - Analysis - PCBs** | 2 | **Brody JB**, **Cancer Supplement.** Volume 109 / Number 12. **2007.** |
| 1 | **Zhang J**, Huang Y, Wang X, et al. **PLOS ONE,** 10, **2015.** | 3 | **Wolff MS**, Toniolo PG. 103 (Suppl 7) :141-145 **EHP. 1995.** |
| 2 | **Leng L, Li J, et al. E**nvironment International 88. 133–141, **2016.** | 4 | **Rodgers KM,** Udesky JO, Rudel RA, Brody JG. Environmental Research 160,152–182. **2018.** |

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## ANNEX 2 – References DDT, DDD, DDE and Organochlorines Compounds (Lindane, Hexachlorobenzene (HCB), Chlordane, ecc.) articles

| N° | Name of researchers / scientific journal | Place and study design | Exposure contaminants | Exposure assessment procedure | Time of sample collecting | Years of the Study interest | Exposure category or level / Risk estimate (95% CI) | Relevant Comment | Methods and possible covariates |
|---|---|---|---|---|---|---|---|---|---|
| 1 | **López-Carrillo L**, Blair A, López-Cervantes M, Cebrián M, Rueda C, Reyes R et al. **Cancer Res, 57(17):3728–32. 1997.** | hospital-based case-control study **Mexico** | DDE (ng/g lipid) 505.46; p,p′-DDT(ng/g lipid) 84.53 | Serum | After diagnosis | 1994-1996 | Not statistically significance | These results do not lend support to the hypothesis that DDT is causally related to breast cancer- | Age, BMI, socio economic characteristics, diet, and occupation. |
| 2 | **Romieu I,** Hernandez-Avila M, Lazcano-Ponce E, Weber JP, Dewailly E. Am J Epidemiol, 152(4):363–70. **2000.** | case-control study **Mexico** | DDE | Serum | After diagnosis | 1990-1995 | After adjustment for age, age at menarche, duration of lactation, Quetelet index, and serum DDT levels, serum DDE levels were positively related to the risk of breast cancer. | The data suggest that high levels of exposure to DDE may increase women's risk of breast cancer, particularly among postmenopausal women. | Age, menarche, lactation, BMI, menopause |
| 3 | **Boada LD,** Zumbado M, Henríquez-Hernández LA, Almeida-González M, Alvarez-León EE, Serra-Majem L et al. Environ Health, 11(1):28. **2012.** | case-control study. Gran Canaria Island, **Spain** | Complex organochlorine pesticides | Serum | After diagnosis | 1999-2001 | OR=1.097; 95% CI 0.420–28.412 | Limitations: not matched by age; cases were significantly older than controls, and few women were exposed | Age, BMI, menopausal status, lactation, and tobacco |
| 4 | **Charlier C**, Albert A, Herman P, Hamoir E, et al. **Occup Environ Med, 60(5):348–51. 2003.** | case control study. Liege, **Belgium** | DDT and hexachlorobenzene (HCB) | Serum | After diagnosis | / | Not statistically significance | Mean levels of total DDT and HCB were significantly higher for breast cancer patients than for controls but Not statistically significance | Age, BMI, menopausal status, blood levels of HCB and total DDT |
| 5 | **Charlier C**, Foidart JM, Pitance F, et al. **Clin Chem Lab Med, 42(2):222–7. 2004.** | case control study. Liege, **Belgium** | DDE and hexachloro benzene HCB | Serum | After diagnosis | 2001 - 2002 | p,p DDE > 0.5 ppb OR 2.21 95% CI (1.41–3.48) HCB> 0.5 ppb OR 4.99, 95% CI (2.95-8.43) | Strengths: sample size; blood draw before surgery Limitations: no BMI information; hospital based controls | Age, BMI, parity, lactation, menopause, HRT, family history |

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| N° | Name of researchers / scientific journal | Place and study design | Exposure contaminants | Exposure assessment procedure | Time of sample collecting | Years of the Study interest | Exposure category or level / Risk estimate (95% CI) | Relevant Comment | Methods and possible covariates |
|---|---|---|---|---|---|---|---|---|---|
| 6 | **Zheng T**, Holford TR, Mayne ST et al. **Cancer Epidemiol Biomarkers Prev, 9(2):167–74. (2000).** | Case–control study. Connecticut, **USA** | DDE and PCBs | Serum Samples | After diagnosis | 1995–1997 | DDE (highest versus lowest quintile adjusted for age, body mass index (BMI) and breastfeeding for DDE: OR = 1.02, 95% CI = (0.61, 1.72), p-trend = 0.74; | No association was identified between DDE and risk of breast cancer | Age, BMI, reproductive risk factors, HRT, dietary fat intake, family history of breast cancer. |
| 7 | **Itoh H**, Iwasaki M, Hanaoka T et al. Cancer Causes Control, 20(5):567–80. **2009.** | Case–control hospital study in Nagano Prefecture. **Japan** | DDT, DDE | Serum Samples | After diagnosis | 2001 - 2005 | IV Quartile median (ng/g lipid) p,p′-DDE:1.02 (0.46–2.26) p,p′-DDT:0.58 (0.27–1.25) o,p′-DDT:0.67 (0.30–1.50) | No association was identified between DDT, DDE and risk of breast cancer | Age, BMI, total lipid concentration in serum, reproductive risk factors, medical history, area, lipid, menopause, smoking, fish and veg consumption, family history of breast cancer |
| 8 | **Wolff MS**, Toniolo PG, Lee RW, et al. **J Natl Cancer Inst 85:648–52**.**1993.** | A prospective cohort study. New York. **USA** | DDE, PCBs | Serum Samples | After diagnosis | 1985 - 1991 | Increase in relative risk of breast cancer for an elevation of serum DDE concentrations from 2.0 ng/mL (10th percentile) to 19.1 ng/mL (90th percentile). | In this population of New York City women, breast cancer was strongly associated with DDE in serum but not with PCBs. | Age, BMI, after adjustment for first-degree family history of breast cancer, lifetime lactation, and age at first full-term pregnancy. |
| 9 | **Gatto NM**, Longnecker MP, Press MF et al. **Causes Control.18:29–39. 2007.** | Case–control study in five **USA** | DDE, DDT, PCBs. | Blood Samples | After diagnosis | 1995-1998 | DDE: OR = 1.02, 95% CI = (0.61, 1.72), p-trend = 0.74; PCBs: OR = 1.01, 95% CI = (0.63,1.63),p-trend = 0.56). | No association was identified between DDT, DDE, PCBs and risk of breast cancer | Age, BMI, lactation, lipid. |
| 10 | **Millikan R**, DeVoto E, Duell EJ, et al. **Cancer Epidemiol Biomarkers Prev. 9(11):1233–40. 2000.** | case-control study **USA** | DDE, PCBs | Plasma | After diagnosis | 1993 – 1996 | DDE, µg/g lipid African-Americans ≥ 1.8 OR 1.41; 95% CI (0.87–2.29) | We observed no overall association between plasma levels of DDE and total PCBs and breast cancer among African-American and white women in North Carolina. | Age, BMI, age-squared, race (all participants), lipid, menopausal status, parity/lactation, HRT, income. |
| 11 | **Gammon MD,** Wolff MS, et al. Vol. 11, 686–697, **Cancer Epidemiology, Biomarkers & Prevention; 2002;** | Case-control study. Long Island, **USA** | DDE, DDT, Chlordane, Dieldrin, PCBs | Blood Samples | After diagnosis | 1996-1997 | No substantial elevation in breast cancer risk was observed in relation to the highest quintile of lipid-adjusted serum levels of organochlorine compounds | No association was identified between DDE, DDT, Chlordane, Dieldrin, PCBs and risk of breast cancer | Age, BMI, race, reproductive history, benign breast disease Interview response rates: cases, 83.2%; controls, 68.0%. |

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| N° | Name of researchers / scientific journal | Place and study design | Exposure contaminants | Exposure assessment procedure | Time of sample collecting | Years of the Study interest | Exposure category or level / Risk estimate (95% CI) | Relevant Comment | Methods and possible covariates |
|---|---|---|---|---|---|---|---|---|---|
| 12 | **Demers A**, Ayotte P, Brisson J et al.**Cancer Epidemiol Biomarkers Prev, 9(2):161–6. 2000.** | Case-control study. **Canada** | DDE, PCBs. | Serum Samples | After diagnosis | 1994–1997 | DDE, ng/g lipid, population controls 282.5 < 427.8 Population OR (95% CI) 1.06 (0.62–1.79) Hospital OR (95% CI) 0.66 (0.37–1.19) | No association was identified between DDE, PCBs and risk of breast cancer | Age, region of residence, BMI, breast feeding duration, age at first child, number of fertile years, family history of breast cancer, and history of benign breast disease. |
| 13 | **Laden F**, Hankinson SE, Wolff MS et al. **Int J Cancer.** 91(4):568–74. **2001.** | nested case-control study. **USA** | DDE and PCBs | Plasma | After and before diagnosis | 1976–1994 | DDE, µg/g lipid 1.466 – 6.054 OR (95% CI) 0.82 (0.49–1.37) | No association was identified between DDE, PCBs and risk of breast cancer | Age, BMI, family history of breast cancer, history of BBD, age at menarche, BMI, lipid, number of children, age at birth of first child, lactation. |
| 14 | **Krieger N,** Wolff MS, Hiatt RA, et al. **J Natl Cancer Inst, 86(8):589–99. 1994.** | 5 small case–control study. San Francisco Bay **USA** | DDE, DDT and PCBs. | Serum Samples | after (or at most 6 months before) diagnosis. | 1964 - 1990 | no significant association was seen between risk of cancer of the breast and serum DDE | The data do not support the hypothesis that exposure to DDE and PCBs increases risk of breast cancer. | BMI, age at menarche, ever vs never pregnant, menopausal status at time of case patient´s diagnosis of breast cancer plus variables matched by design. |
| 15 | **Hunter DJ,** Hankinson SE, Colditz GA,et al. **N Engl J Med, 337(18):1253–8. 1997.** | case-control study **USA** | DDE | Plasma | After diagnosis | 1976 - 1992 | DDE, ppb > 9.46 (OR, 0.72; 95% CI, 0.37–1.4). | Our data do not support the hypothesis that exposure to DDE increases the risk of breast cancer. | History of breast cancer in a mother or sister of benign breast disease, age at menarche, number of children and age at birth of first child, duration of lactation, BMI, plus variables matched by design |
| 16 | **Dorgan JF**, Brock JW, Rothman N et al. **Cancer Causes Control. 10(1):1–11. 1999.** | nested case-control study **USA** | DDT, PCBs | Blood samples | before diagnosis | 1977 - 1987 | No association found for DDE and DDT in ng/g lipid in serum of exposed cases | Results of this study do not support a role for organochlorine pesticides and PCBs in breast cancer etiology. | Age, BMI, menopausal status, family history, estrogen use, parity, age at menarche |

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| N° | Name of researchers / scientific journal | Place and study design | Exposure contaminants | Exposure assessment procedure | Time of sample collecting | Years of the Study interest | Exposure category or level / Risk estimate (95% CI) | Relevant Comment | Methods and possible covariates |
|---|---|---|---|---|---|---|---|---|---|
| 17 | **Helzlsouer KJ,** Alberg AJ, Huang HY, et al. **Cancer Epidemiol Biomarkers Prev, 8(6):525–32. 1999.** | Nested case-control study. **USA** | DDE, DDT, PCBs | Serum | Strengths: serum collected up to 20 yrs before diagnosis; | 1974 - 1994 | No association found for DDE in ng/g lipid in serum of e exposure category or level (1974 and 1989) | Even after 20 years of follow-up, exposure to relatively high concentrations of DDE or PCBs showed no evidence of contributing to an increased risk of breast cancer. | Age, history of breast cancer, BMI at age 20 yrs or current age at menarche, age at first birth, duration of lactation plus matching variables |
| 18 | **Cohn BA, EHP, 2007.** | Nested case–control study. Oakland **California** | DDT, DDE, and metabolites | Blood Samples (young women) mean age of 26 years | Before diagnosis | 1959–1967 | Age < 14 yrs in 1945 p,p′-DDT, μg/L 8.09–13.90 (OR, 2.5; 95% CI,1.0–6.3) | Exposure to p,p´-DDT early in life may increase breast cancer risk. | Age (matching), BMI, blood lipids (total cholesterol, total triglycerides), parity, year of blood draw, breast-feeding after current pregnancy 10 congeners measured. |
| 19 | **Cohn BA,** La Merrill M, Krigbaum NY et al. **J Clin Endocrinol Metab, 100(8):2865–72. 2015.** | Nested case–control study. Oakland. **California** | DDT | Serum post partum | Before diagnosis | 1959–1967 | Maternal o,p -DDT predicted daughters' breast cancer (odds ratio fourth quartile vs first (OR, 3.7; 95% CI, 1.5–9.0). | This prospective human study links measured DDT exposure in utero to risk of breast cancer. | Age, BMI, maternal cholesterol and triglycerides, maternal overweight in early pregnancy and maternal history of breast cancer |
| 20 | **Hoyer AP,** Jørgensen T, Grandjean P et al. **Cancer Causes Control, 11(2):177–84. 2000.** | nested case-control study Copenhagen. **Denmark** | DDT | Serum | After diagnosis | 1976 - 1992 | p,p' DDT ng/g OR= 3.6; 95% CI, 1.1–12.2) | A high serum concentration of p,p'-DDT over the course of the two examinations was associated with a more than three-fold significantly increased risk of breast cancer. | Age, BMI, breast cancer characteristics included tumor size, degree of spread, and stage of disease. |
| 21 | **Ward EM,** Schulte P, Grajewski B et al. **Cancer Epidemiol Biomarkers Prev. 9(12):1357-67. 2000.** | nested case-control study **Norway** | DDE and PCBs | Serum | before diagnosis | 1973 - 1991 | no significant association was seen between risk of cancer of the breast and serum DDE | This is a case-control study of serum organochlorine levels in relation to breast cancer risk. | Age, BMI, occupational category, age at first birth, number of births prior to donation of blood sample, region of residence, and region of birth, lipid concentration in serum. |
| 22 | **Iwasaki M**, Inoue M, Sasazuki S, et al. **Science Total Environment 402(2–3):176–183. 2008.** | Nested case–control study. **Japan** | DDT, DDE, HCB, β-HCH. | Plasma | Before diagnosis | 1990 - 1994 | Adjusted ORs for p,p'-DDT, HCB,and β-HCH were less than 1. For p,p'-DDE, adjusted OR for the highest versus lowest quartile was 1.48 (95% confidence interval 0.70-3.13; p for trend=0.25). | We found no statistically significant positive association between plasma organochlorine level and breast cancer risk. | Age at menarche, menopausal status at baseline, number of births, age at first birth, height (continuous), BMI, alcohol consumption |

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| N° | Name of researchers / scientific journal | Place and study design | Exposure contaminants | Exposure assessment procedure | Time of sample collecting | Years of the Study interest | Exposure category or level / Risk estimate (95% CI) | Relevant Comment | Methods and possible covariates |
|---|---|---|---|---|---|---|---|---|---|
| 23 | **Raaschou-Nielsen O,** Pavuk M, LeBlanc A, et al. **Cancer Epidemiol Biomarkers Prev. 14(1):67–74. 2005.** | Nested case-control study **Denmark** | DDE | Adipose breast tissue | Tissue was sampled up to 6.5 years before the breast cancer diagnosis | 1993 – 1997 | No association found for DDE and DDT in ng/g lipid in serum of exposed cases | We found no indication of higher breast cancer risk in association with higher adipose tissue concentrations of any of the chlorinated pesticides. | Age, education, BMI, lipid, alcohol, number of children, age at birth of first child, lactation, HRT, history of BBD. |
| 24 | **Wolff MS**, Berkowitz GS, Brower S et al. **Environ Res, 84(2):151–61. 2000b** | A hospital-based case-control study. NY **USA** | DDE, DDT | blood serum or adipose tissue | After diagnosis | 1985 - 1994 | DDE: 664–1172 ng/g OR= 0.81;95% CI,0.35–1.87 | We found no statistically significant positive association between plasma organochlorine level and breast cancer risk. | Age at menarche, number of full-term pregnancies, age at first full-term pregnancy, family history of breast cancer, lifetime history of lactation, height), BMI, BMI-menopausal status interaction |
| 25 | **Olaya-Contreras P,** Rodríguez-Villamil J, Posso-Valencia HJ, et al. **Cad Saude Publica, 14:Suppl 3: 125–32. 1998.** | Bogota **Colombia** | DDT, DDD and DDE | Serum | After diagnosis | 1995–1996 | DDE, ng/mL (higher category of DDE exposure) 1.97–19.20 OR=1.95; 95% CI,1.10–3.52 | We confirm that serum DDE levels bear a positive association to risk of breast cancer | Age, family history, BMI, parity, menopause, breast cancer history, lactation |
| 26 | **Moysich KB**, Ambrosone CB, Vena JE, et al. **Cancer Epidemiol Biomarkers Prev. 7(3):181–8. 1998.** | case-control study **USA** | DDE, HCB,PCBs | Serum | After diagnosis | 1986-1991 | DDE, ng/g lipid 3rd tertile OR=1.34; 95% CI, 0.71–2.55 | Elevated serum levels od DDE were not associated with breast cancer risk | Age, education, family history of breast cancer, parity, quetelet index, lactation, age at first birth, years since last pregnancy, fruit and vegetable intake, lipid. |
| 27 | **Mendonca GA**, Eluf-Neto J, Andrada-Serpa MJ, et al. **Int J Cancer, 3(5):596–600. 1999.** | hospital-based case-control study. **Brasil** | DDE | Serum | After diagnosis | 1995–1996 | Serum DDE, ng/mL ≥ 7.6 OR=0.83; 95% CI, 0.4–1.60 | Exposure to organochlorinated pesticides measured by history or serum analysis was thus not a risk factor for breast cancer. | Age, lactation, education, parity, smoking, family history, breast size |
| 28 | **Dello Iacovo R**, Celentano E, Strollo AM, et al. **Adv Exp Med Biol, 472:57–66. 1999.** | case-control study. Naples **Italy** | DDE | Serum | After diagnosis | 1993-1998 | Serum DDE, ng/mL > 10.2 OR=1.24; 95% CI, 0.7–2.2 | Strengths: sizeable sample; > 30% having DDE > 10 ng/mL | Age, BMI, lactation, parity, serum lipids, education, smoking, menopause |
| 29 | **Wolff MS**, Zeleniuch-Jacquotte A, Dubin N, et al. **Cancer Epidemiol Biomarkers Prev, 9(3):271–7. 2000a** | hospital case-control study **USA** | DDE and PCBs | Serum | Before diagnosis | 1994 - 1995 | DDE, µg/g lipid 0.034–1.3 OR=1.34; 95% CI, 0.82–2.20 | In summary, we found no association between organochlorine compounds and breast cancer | Age, age-square, menopause, race, strata, lactation, HRT, parity |

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| N° | Name of researchers / scientific journal | Place and study design | Exposure contaminants | Exposure assessment procedure | Time of sample collecting | Years of the Study interest | Exposure category or level / Risk estimate (95% CI) | Relevant Comment | Methods and possible covariates |
|---|---|---|---|---|---|---|---|---|---|
| 30 | **Schecter A**, Toniolo P, Dai LC, Thuy LT, et al. **Arch Environ Contam Toxicol, 33(4):453–6. 1997.** | Small hospital-based case-control study. Hanoi. **Vietnam** | DDT and DDE | Serum | After diagnosis | 1994 | DDE, ng/mL 3rd vs 1st tertile OR =1.21; 95% CI, 0.15–9.65 | levels and breast cancer risk in our study. | Age, BMI, age at menarche, parity, lactation, weight |
| 31 | **Soliman AS**, Wang X, Di Giovanni J, Eissa S, et al. **Environ Res, 92(2):110–7. 2003.** | case-control study **Egypt** | DDE and beta - HCH | Serum | After diagnosis | N. R. | DDE (ppb) > 4.7 OR =1.41; 95% CI, 0.63–3.19 | Organochlorine serum level was not a risk factor of breast cancer in this population. | Age, lactation, menopausal status, residence. |
| 32 | **Pavuk M**, Cerhan JR, Lynch CF, et al. **J Expo Anal. Environ Epidemiol, 13(4):267–75. 2003.** | case-control study. **Slovakia** | **DDE, DDT,** and hexachlorobenzene (HCB) andaA total of 15 individual **PCB congeners.** | Serum | After diagnosis | 1997–1999 | DDE, ng/g lipid 4389–19912 OR=3.04; 95% CI, 0.65–14.3 DDT, ng/g lipid 137–562 OR=1.19; 95% CI, 0.27–5.23 | Organochlorine compounds was positively associated with risk, but not statistically significant | Age, menarche, education, alcohol intake, smoking. |
| 33 | **Rubin CH**, Lanier A, Kieszak S, et al. **International journal of circumpolar health** 65(1):18–27. **2006.** | Case-control study; **Alaska** | DDT, DDE and 13 other chlorinated pesticides, PCBs (28 congeners). | Serum Samples | Before diagnosis | 1983-1987 | DDE (ppb) > 9.62 OR=1.43; 95% CI, 0.46–4.47 | we found no statistically significant association between organoclorine compounds and breast cancer | Parity, family history of breast cancer, race, triglycerides, cholesterol. |
| 34 | **van't Veer P**, Lobbezoo IE, Martín-Moreno JM, et al. **BMJ, 315(7100):81–5. 1997.** | multicentre case-control study. **Germany, the Netherlands, Ireland, Switzerland, and Spain** | DDE, DDT | Adipose tissue | After diagnosis | 1991–1992 | DDE, µg/g 0.87- 1.89 OR= 1.14; 95% CI, 0.62–2.12 | This study does not support the hypothesis that DDE increases risk of breast cancer in postmenopausal women in Europe. | Age, centre, BMI, age at first birth, alcohol consumption |
| 35 | **Liljegren G**, Hardell L, Lindström G, et al.. **Eur J Cancer Prev. 1998.** | Case-control study. **Sweden** | DDE, HCB and PCBs | Adipose tissue | After diagnosis | 1993–1995 | DDE, ng/g lipid > 700 OR=0.4; 95% CI, 0.1–1.2 | No significant difference for the sum of non co-planar DDE or PCBs was found between cases and controls. | Age,BMI, menopausal status, parity. |
| 36 | **Zheng T**, Holford TR, Mayne ST, et al. Cancer, 85(10):2212–8.1999. | case-control study Connecticut, **USA.** | DDE and DDT | Adipose tissue | After diagnosis | 1994–1997 | DDE, ng/g lipid 412.6–779.2 OR=1.3; 95% CI, 0.7–2.2 | These results do not support an association between adipose tissue levels of DDE and DDT and breast cancer risk. | Age, BMI, lifetime months of lactation, age at menarche, age at FFTP, menopausal status. |

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| N° | Name of researchers / scientific journal | Place and study design | Exposure contaminants | Exposure assessment procedure | Time of sample collecting | Years of the Study interest | Exposure category or level / Risk estimate (95% CI) | Relevant Comment | Methods and possible covariates |
|---|---|---|---|---|---|---|---|---|---|
| 37 | Aronson KJ, Miller AB, Woolcott CG, et al. **Cancer Epidemiol Biomarkers Prev.9(1):55–63. 2000.** | case-control study **Canada** | DDE and PCBs | Adipose tissue | Before diagnosis | 1995 – 1997 | DDE, µg/kg lipid > 1390 OR=1.62; 95% CI, 0.84–3.11 | These results do not support an association between adipose tissue levels of DDE and PCBs and breast cancer risk. | Age, study site, menopausal status, present use of HRT, ethnicity, BMI fat and alcohol intake |
| 38 | Ibarluzea JM, Fernández MF, Santa-Marina L, et al. **Cancer Causes Control, 15(6):591–600. 2004.** | Hospital case-control study. **Spain** | DDE, aldrin, endosulfan and lindane | Adipose tissue | After diagnosis | 1996–1998 | DDE, ng/g lipid ≥ 675.98 OR, 1.22; 95% CI, 0.68–2.21 | DDE was positively associated with risk, but not statistically significant | Age, reference hospital, number of children, age at FFTP, family history of breast cancer, and alcohol and tobacco consumption |
| 39 | **Hoyer AP**, Jorgensen T, Rank F, et al. **BMC Cancer. 1:8. 2001.** | Nested case-control study. **Denmark** | Dieldrin, HCB, PCBs | Blood Samples | Before diagnosis | 1976 - 1978 | Organochlorines in quartiles (ng/mL) Dieldrin >57.11 Estrogen receptor negative OR=7.6; 95% CI,1.3-46.1 | we observed increased breast cancer risk associated with exposure to dieldrin derived from women who developed an estrogen receptor negative (ERN) tumor | Breast cancer characteristics included tumor size, degree of spread, and stage of disease |
| 40 | Hoyer AP, Grandjean P, Jørgensen T et al. **The Lancet 352(9143): 1816 – 20.1998.** | nested case-control study **Denmark** | DDT, Dieldrin, PCBs | Serum | After diagnosis | 1976 – 1995 | DDT OR=0·84; 95% CI,0·49–1·45 | Our results support the hypothesis that organochlorine compounds such as dieldrin, which have oestrogenic properties, may increase the risk of breast cancer. | age, weight, height, number of children, alcohol, smoking, lipid, physical activity, menopausal status, household income, marital status, education. |

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**ANNEX 2 – References DDT, DDD, DDE and Organochlorines Compounds (Lindane, Hexachlorobenzene (HCB), Chlordane, ecc.) monographs IARC, reviews, meta – analysis.**

| | MONOGRAPHS IARC - DDT | N° | REVIEWS - DDT, DDD, DDE and Organochlorine Compounds |
|---|---|---|---|
| 1 | **IARC Monographs DDT, LINDANE, AND 2,4-D Vol. 113; 2018** | 1 | **López-Cervantes M et al. Environ Health Perspect. 2004 Feb;112(2):207-14.** |
| | **Meta - Analysis - DDT, DDD, DDE** | 2 | **Wolff MS**, Toniolo PG. 103 (Suppl 7) :141-145 **EHP. 1995.** |
| 1 | **Park JH,** Cha ES, Ko Y, et al. Osong Public Health Res Perspect. Apr;5(2):77-84. **2014.** | 3 | **Snedeker SM**, **EHP. 2001.** |
| | | 4 | **Gray JM** , Rasanayagam S, Engel C and Rizzo J. **Environmental Health, 16:94; 2017.** |
| | | 5 | **Calle EE,** Frumkin H, Henley SJ, et al. **CA Cancer J Clin. Sep-Oct;52(5):301-9. 2002.** |
| | | 6 | **Macon MB**, Fenton SE. J Mammary Gland Biol Neoplasia. Mar;18(1):43-61. **2013.** |
| | | 7 | **Gray JM** , Rasanayagam S, Engel C and Rizzo J. Environmental Health, 16:94; **2017.** |

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## ANNEX 3 – References Dioxins (TCDD) articles.

| N° | Name of researchers / scientific journal | Place and study design | Exposure contaminants | Exposure assessment procedure | Time of sample collecting | Years of the Study interest | Exposure category or level / Risk estimate (95% CI) | Relevant Comment | Methods and possible covariates |
|---|---|---|---|---|---|---|---|---|---|
| 1 | **Warner M**, Mocarelli P, Samuels S, **Environ Health Perspect. Dec; 119(12): 1700-5. 2011.** | Cohort study. Seveso (MI). **Italy** | TCDD | Blood draw | / | 1996 - 2008 | For breast cancer, the HR was increased, but not significantly (adjusted HR = 1.44; 95% CI: 0.89, 2.33). | Individual serum TCDD is significantly positively related with all cancer incidence in the SWHS cohort, more than 30 years later. This all-female study adds to the epidemiologic evidence that TCDD is a multisite carcinogen. | Individual TCDD concentration was measured in archived serum by high-resolution mass spectrometry. A total of 833 women participated in the 2008 follow-up study. We examined the relation of serum TCDD with cancer incidence |
| 2 | **Pesatori AC**, Consonni D, Rubagotti M, Grillo P, Bertazzi PA**. Environ Health. 8:39. 2009.** | Cohort study**.** Seveso (MI). **Italy** | 2,3,7,8-tetrachloro dibenzo-p-dioxin (TCDD); | Blood samples | / | 1977-1996 | An increased risk of breast cancer was detected in zone A females after 15 years since the accident (five cases, RR, 2.57; 95% CI, 1.07-6.20). | The elevated risk of breast cancer in zone A females after 15 years since the accident deserves further and thorough investigation. | Gender-, age-, and period-adjusted rate ratios (RR) and 95% confidence intervals (95% CI) were calculated . |
| 3 | **Bencko V**, Rames J, Ondrusova M, at al. **Neoplasma. 2009;56(4):353-7. 2009.** | Two ecological studies in **Slovak Republic and in Czech Republic.** | TCDD and PCBs | **/** | / | 1987-1996 | 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. | The results of our analysis points to substantial potential problems of risk assessment for cancer incidence in populations exposed to xenobiotic, or more generally, as it relates to a wide spectrum of confounding of cancer risk factors. | The age-adjusted world standard ratio (WSR) incidence of malignant breast tumors in females were compared for whole the Slovak Republic and the Michalovce District. For |
| 4 | **Warner M**, Eskenazi B, Mocarelli P, et al. Environ Health Perspect. Jul;110(7):625-8. **2002.** | Cohort study. Seveso (MI). **Italy** | TCDD | serum samples | before and after diagnosis | 1996-1998 | We observed a statistically significant, dose response–increased risk for breast cancer incidence with individual serum TCDD level among women in the Seveso Women's Health Study. | Continued follow-up of the cohort will help shed light on the possible role of TCDD in the pathogenesis of breast cancer | We examined the effect of potential confounders like gravidity, parity, age at first pregnancy, age at last pregnancy, lactation, family history of breast cancer, age at menarche, current body mass index. |

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| N° | Name of researchers / scientific journal | Place and study design | Exposure contaminants | Exposure assessment procedure | Time of sample collecting | Years of the Study interest | Exposure category or level / Risk estimate (95% CI) | Relevant Comment | Methods and possible covariates |
|---|---|---|---|---|---|---|---|---|---|
| 5 | **Revich B**, Aksel E, Ushakova T, et al. **Chemosphere. May - Jun;43(4-7):951-66. 2001.** | Ecological study. Chapaevsk, **Russia.** | Dioxins; | blood samples and human milk | / | 1997-1998 | The SMR is higher for breast cancer. Chapaevsk women have a higher risk overall due to breast cancer 2.1 (C.I. 1.6-2.7) | We confirm that blood dioxins levels bear a positive association to risk of breast cancer | Sampling of human milk was carried out. The average age of the mothers was 22.0 years. All surveyed mothers classified their diet as mixed and diary products every day. All respondents never smoked as they self-reported in the interview. |
| 6 | **Bertazzi PA,** Zocchetti C, Guercilena S, Consonni D, Tironi A, Landi MT, Pesatori AC. **Epidemiology**. Nov;8(6):646-52. **1997.** | A 15-year mortality study. **Italy** | 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD). | / | / | 1976-1991 | We found no increase for all-cancer mortality or major specific sites (for example, respiratory among males, breast among females). | | age, BMI, smoking, lipid, physical activity, menopausal status. |
| 7 | **Bertazzi PA**, Pesatori AC, Consonni D, Tironi A, Landi MT, Zocchetti C. Vol. 4, No. 5, pp. 398-406. **Epidemiology. 1993.** | Cohort study. Seveso (MI). **Italy** | 2,3,7,8-Tetrachlorodibenzo-para-Dioxin (TCDD). | serum | / | 1977-1986. | Breast cancer among females was below expectations in the most contaminated zones. | | age, BMI, smoking, lipid, physical activity, menopausal status. |
| 8 | **Viel JF**, Clément MC, Hägi M, Grandjean S, Challier B, Danzon A. **Int J Health Geogr. 28;7:4. 2008.** | Case-control study. **France** | Dioxins | / | / | 1996 - 2002 | no increased or decreased risk was found for any dioxin exposure category. Conversely, women over 60 years old living in the highest exposed zone were 0.31 time less likely (95% confidence interval, 0.08–0.89) to develop invasive breast cancer. | Before speculating that this decreased risk reflects a dioxin anti-estrogenic activity with greater effect on late-onset acquired breast cancer, some residual confounding must be envisaged. | age, BMI, smoking, lipid, physical activity, menopausal status. |

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| N° | Name of researchers / scientific journal | Place and study design | Exposure contaminants | Exposure assessment procedure | Time of sample collecting | Years of the Study interest | Exposure category or level / Risk estimate (95% CI) | Relevant Comment | Methods and possible covariates |
|---|---|---|---|---|---|---|---|---|---|
| 9 | **Reynolds P**, Hurley SE, Petreas M, et al. **Cancer Causes Control; 16(5):525-35. 2005.** | A hospital-based case-control study. In the San Francisco Bay Area. **USA** | PCDD/PCDFs. | Breast adipose tissue | at (or near) the time of diagnosis. | during the mid-1990s | One notable exception was octachlorodibenzo-p-dioxin (OCDD), for which the odds ratio for the second and third tertiles appeared modestly elevated (OR = 1.22, 95% CI: 0.47:3.16 and OR = 1.62, 95% CI: 0.64:4.12, respectively), though the test for trend was not significant (p = 0.36). | Breast cancer risk was not associated with adipose levels of PCDD/PCDFs. More study is suggested among women of color who may have higher body burden levels of these compounds. | Invasive breast cancer cases in women ≥20 year of age were identified from the California Cancer Registry, for 1988-1997. Neighbourhood SES and urbanization were derived from U.S. Census data. |
| 10 | **Verkasalo PK**, Kokki E, Pukkala E, et al. **Environ Health Perspect. 112(9):1026–1031. 2004.** | The ecological study population. **Finland** | PCDD/Fs | / | / | 1981 - 2000 | RR 1.15 (1.03 – 1.28 95% C.I.) in those living 1.0 – 4.9 Km from the river. | We also observed increases for cancers of the uterine cervix and corpus, breast, and lung, and BCCs among those living 1.0 – 4.9 km from the river. | All variables were classified according in 500 m × 500 m grid squares. For each grid square in Finland, observed cancers were counted by sex, age, and SES. |
| 11 | **Hardell L**, Lindström G, Liljegren G, et al. **Eur J Cancer Prev. Oct;5(5):351-7. 1996.** | Case control study. **Sweden** | PCDD/Fs | Breast adipose tissue | After diagnosis | 1993 - 1995 | OR was obtained for OCDD: 401-1000 pg/g lipid yielded OR 3.8, 95% confidence interval (CI) 0.4-39 | Breast tissue concentration of OCDD was increased in cancer patients but not statistically significant, whereas the concentrations of other PCDDs and PCDFs were equal in cases and controls. | age, BMI, smoking, breast adipose tissue |
| 12 | **Dai D,** Oyana TJ. **Environ Health. 2008.** | Ecological study. Michigan, **USA.** | Dioxins | / | / | 1985 - 2002 | Preliminary statistical analysis suggests that there is a strong association between elevated levels of breast cancer incidence and aging, particularly among females residing in the city of Midland or near areas contaminated with high dioxins levels. | Increased breast cancer incidences are spatially associated with soil dioxin contamination. | GIS analysis supported; cancer registry in the MDCH; Each case includes information on patient's gender, ZIP code of a patient's residence, year of diagnosis, primary site, stage at diagnosis, and age group; No socio-economic status |

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| N° | Name of researchers / scientific journal | Place and study design | Exposure contaminants | Exposure assessment procedure | Time of sample collecting | Years of the Study interest | Exposure category or level / Risk estimate (95% CI) | Relevant Comment | Methods and possible covariates |
|---|---|---|---|---|---|---|---|---|---|
| 13 | **Guajardo OA and Oyana TJ. Journal of Environmental and Public Health Volume.** Article ID 316249, 16 pages. **2009.** | Ecological study. Michigan, **USA.** | Dioxins | / | / | 1985 - 2002 | ZIP codes 48640 OR = 1.76, (95% CI 1.316 – 2.355) ZIP codes 48603 OR = 1.65, (95% CI 1.238 – 2.202) ZIP codes 48734 OR = 1.88, (95% CI 1.349–2.630) | the spatial distribution of breast and lung cancer incidence rates is non homogeneous; a significant positive association between possible exposure to environmental pollution and risk of breast and lung cancer was found; | the socioeconomic factors, such as race and residency at the same location, are more likely to explain spatial variability of cancer incidences. |

## ANNEX 3 – References Dioxins (TCDD) monographs IARC, reviews, meta – analysis.

| | MONOGRAPHS IARC - Dioxin (TCDD) | N° | REVIEWS – Dioxin (TCDD) |
|---|---|---|---|
| 1 | **IARC Monographs Dioxin (TCDD) Vol. 69; 1997** | 1 | **Laden F,** Hunter DJ. **Annu Rev Public Health. 19:101-23.1998.** |
| 2 | **IARC Monographs Dioxin (TCDD) Vol. 100F. 2012.** | 2 | **Birnbaum LS**, Fenton SE. **Environ Health Perspect. 111(4): 389–394. EHP. 2003.** |
| | | 3 | **Boffetta P,** Mundt KA, Adami HO, et al. **Crit Rev Toxicol. 41(7):622–36. 2011.** |
| | | 4 | **Jenkins S,** Betancourt AM, Wang J, Lamartiniere CA. **J Steroid Biochem Mol Biol. Apr;129 (3-5):191-200. 2012.** |
| | | 5 | **Macon MB, J Mammary Gland Biol Neoplasia. 2013.** |

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## ANNEX 4 – References Polycyclic Aromatic Hydrocarbons (PAH) articles.

| N° | Name of researchers / scientific journal | Place and study design | Exposure contaminants | Exposure assessment procedure | Time of sample collecting | Years of the Study interest | Exposure category or level / Risk estimate (95% CI) | Relevant Comment | Methods and possible covariates |
|---|---|---|---|---|---|---|---|---|---|
| 1 | **Shantakumar SJ**, Gammon MD, Eng SM, et al.. **J Expo Anal Environ Epidemiol. 15(6):482-90.2005.** | Population - based study. Long Island, New York. **USA** | PAH | blood samples | After diagnosis | 1996-1997 | Women who donated blood in summer and fall had increased odds of detectable PAH-DNA adducts OR = 2.65, 95% confidence interval (CI)=1.69, 4.17; | These data suggest that PAH-DNA adducts detected in a population-based sample of adult women with ambient exposure levels reflect some key residential PAH exposure sources assessed in this study, such as cigarette smoking. | Ambient PAH exposure at the current residence was estimated using geographic modeling Environmental home samples of dust and soil were collected on a random subset of long-term residents (15þ years). A questionnaire, including a dietary history; environmental home samples; and geographic modeling. |
| 2 | **Beyea J,** Hatch M, Stellman SD. **Environmental Health Perspectives. Vol. 114, N° 7 2006** | population-based study Long Island, New York. **USA** | PAHs | blood samples | / | 1996 - 1997 | This study indicates that in developing inhalation exposure estimates it is necessary to account for emissions at intersections to fully determine the spatial distribution of PAH exposure. | This study indicates that in developing inhalation exposure estimates it is necessary to account for emissions at intersections to fully determine the spatial distribution of PAH exposure. | We have constructed a geographic model for airborne polycyclic aromatic hydrocarbons (PAHs) from traffic that is being used in a population-based, case–control epidemiologic study involving about 3,000 women on Long Island, New York, known as the Long Island Breast Cancer Study Project |

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| N° | Name of researchers / scientific journal | Place and study design | Exposure contaminants | Exposure assessment procedure | Time of sample collecting | Years of the Study interest | Exposure category or level / Risk estimate (95% CI) | Relevant Comment | Methods and possible covariates |
|---|---|---|---|---|---|---|---|---|---|
| 3 | **Gammon MD,** Santella RM, Neugut AI, et al. **Cancer Epidemiol Biomarkers Prev 11(8): 677–685.** 2002. | Case-control study. in Long Island, New York. **USA** | PAH. | blood samples | After diagnosis | 1996 - 1997 | The age-adjusted odds ratio (OR) for breast cancer in relation to the highest quintile of adduct levels compared with the lowest was 1.51 [95% confidence interval (CI), 1.04-2.20], | These data indicate that PAH-DNA adduct formation may influence breast cancer development, although the association does not appear to be dose dependent and may have a threshold effect. | women include lower parity, late age at first birth, little or no breast feeding, and family history of breast cancer. Factors associated with an increased probability include white or other race, alcohol use, ever breastfed, ever use of hormone replacement therapy, ever use of oral contraceptives, and ever had a mammogram. |
| 4 | **Gammon MD**, Sagiv SK, Eng SM, et al. **Arch Environ Health, 59(12):640-9.** 2004. | Case-control study. in Long Island, New York. **USA** | PAH | blood samples | After diagnosis | 1996 - 1997 | The odds ratio for breast cancer was elevated in relation to detectable PAH-DNA adducts (1.29 as compared with non detectable adduct levels; 95% confidence interval = 1.05, 1.58). | These data indicate that PAH-DNA adduct formation may influence breast cancer development, although the association does not appear to be dose dependent and may have a threshold effect. | women include lower parity, late age at first birth, little or no breast feeding, and family history of breast cancer. Factors associated with an increased probability include white or other race, alcohol use, ever breastfed, ever use of hormone replacement therapy, ever use of oral contraceptives, and ever had a mammogram. |

| N° | Name of researchers / scientific journal | Place and study design | Exposure contaminants | Exposure assessment procedure | Time of sample collecting | Years of the Study interest | Exposure category or level / Risk estimate (95% CI) | Relevant Comment | Methods and possible covariates |
|---|---|---|---|---|---|---|---|---|---|
| 5 | **Terry MB**, Gammon MD, Zhang FF, et al. **Cancer Epidemiol Biomarkers Prev. 13:2053–2058. 2004.** | Case-control study. In Long Island, NY. **USA** | PAH | blood samples | After diagnosis | 1996-1997 | Overall, we found a modest, statistically significant association between those subjects with at least one variant Gln allele at exon 23 of the XPD gene and breast cancer risk (OR, 1.21; 95% CI, 1.01-1.44). | Overall, this study suggests that those individuals with this polymorphism in the XPD gene may face an increased risk of breast cancer from PAH-DNA adducts and cigarette smoking. | Respondents were asked about their pregnancy, occupational, and residential history; their use of pesticides in their home or on a farm; electrical appliance use; lifetime history of consumption of smoked or grilled foods; medical history; family history of cancer; body size changes by decade; recreational physical activities; cigarette smoking; alcohol use; menstrual history; use of exogenous hormones; and demographic characteristics |
| 6 | **Sagiv SK**, Gaudet MM, Eng SM, et al.. **Environ Res. 109(3): 287–291. 2009.** | A survival analysis In Long Island. **USA** | PAH | blood samples | After diagnosis | 1996 - 1997 | there are not evidence that all-cause mortality (HR) = 0.88; 95% confidence interval (CI): 0.57–1.37), or breast cancer mortality (HR = 1.20; 95% CI: 0.63–2.28) was strongly associated with detectable PAH-DNA | Results from this large population-based study do not provide strong support for an association between detectable PAH-DNA adducts and survival among women with BC, except perhaps among those receiving radiation treatment. | case-control questionnaire, including family history of breast cancer; body size; physical activity; menstrual and reproductive histories; exogenous hormone use; active and passive cigarette smoking; and alcohol consumption. Medical records were abstracted for tumor characteristics including estrogen/ progesterone receptor |

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| N° | Name of researchers / scientific journal | Place and study design | Exposure contaminants | Exposure assessment procedure | Time of sample collecting | Years of the Study interest | Exposure category or level / Risk estimate (95% CI) | Relevant Comment | Methods and possible covariates |
|---|---|---|---|---|---|---|---|---|---|
| 7 | **Burdick AD**, Davis II JW, Liu KJ, et al. **Cancer Research 63, 7825–7833. 2003.** | Study of human mammary epithelial cells and the human mammary epithelial cell line MCF-10A. | PAHs | / | / | 2003 | / | Taken together, these data indicate that BPQs, through the generation of hydrogen peroxide, activate the EGFR in MCF-10A cells, leading to increased cell number under EGF-deficient conditions. | Benzo(a)pyrene Quinones Increase Cell Proliferation, Generate Reactive Oxygen Species, and Transactivate the Epidermal Growth Factor Receptor in Breast Epithelial Cells |
| 8 | **Plıskova M**, Vondrácek J, Vojtesek B, et al. **Toxicological Sciences 83, 246–256. 2005.** | Study of deregulation of Cell Proliferation by Polycyclic Aromatic Hydrocarbons in Human Breast Carcinoma MCF-7 Cells | PAHs | / | / | 2005 | / | In the present study, we found that two PAHs, benz[a]anthracene (BaA) and BaP, can stimulate proliferation of human breast carcinoma MCF-7 cells at concentrations 100 nM and higher. | Deregulation of Cell Proliferation by Polycyclic Aromatic Hydrocarbons in Human Breast Carcinoma MCF-7 Cells Reflects Both Genotoxic and Nongenotoxic Events |
| 9 | **Bonner MR,** Han D, Nie J, et al. **Cancer Epidemiol Biomarkers Prev 2005;14(1). 2005.** | Case -control study. In Western New York. **USA** | PAHs and TSP | / | / | 1996-2001 | For risk associated with estimated residential TSP concentrations on a continuous scale, in postmenopausal women, we observed a 20% increase in the odds ratio for every 30 µg/m³ increase in TSP concentration (adjusted OR, 1.20; 95% CI, 1.04-1.38). | Our study suggests that exposure in early life to high levels of PAHs may increase the risk of post menopausal breast cancer; however, other confounders related to geography cannot be ruled out. | Using extensive in-person interviews and self-administered questionnaires, participants provided information regarding medical history, diet, alcohol consumption, smoking history, lifetime passive smoke exposure, occupational history, and residential history. Residential histories were reported by the subject dating back to birth. |

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| N° | Name of researchers / scientific journal | Place and study design | Exposure contaminants | Exposure assessment procedure | Time of sample collecting | Years of the Study interest | Exposure category or level / Risk estimate (95% CI) | Relevant Comment | Methods and possible covariates |
|---|---|---|---|---|---|---|---|---|---|
| 10 | **Perera F**, Rundle A. **Cancer Epidemiol Biomarkers Prev. 12(1):75-6. 2003.** | Letters to the editor | PAHs | / | / | / | significantly associated with breast cancer (odds ratio 2.56, 96% confidence interval 1.05–6.24; Carcinogenesis, Vol. 21, pp. 1281–1289, 2000) | / | / |
| 11 | **Kulldorff M,** Feuer EJ, Miller BA, et al. Am J Epidemiol. Jul 15;146(2):161-70.**1997.** | A geographic analysis. In the northeast **USA** | PAHs | Breast cancer clusters in the northeast United States | / | 1988–1992 | The New York City-Philadelphia metropolitan area had an excess of deaths among younger women at 6.9 percent compared with an excess of 7.4 percent in the older group. | The several known and hypothesized risk factors for which we could not adjust and that may explain the detected cluster are most notably age at first birth, age at menarche, age at menopause, breastfeeding, genetic mutations, and environmental factors. | The basic analysis is adjusted for age, with further analyses examining how the results are affected by incorporating race, urbanicity, and parity as confounding variables. |
| 12 | **Shen J**, Liao Y, Hopper JL, et al. Terry MB. Br J Cancer. 116(9):1229-1233. **2017.** | A prospective nested case-control study. New York **USA** | PAHs -albumin adducts | blood samples | After diagnosis | NR | Women with detectable levels of PAH had a twofold association with breast cancer risk (**OR = 2.04; 95% CI = 1.06–3.93**) relative to women with non-detectable levels. | These results support that family-based cohorts can be an efficient way to examine gene–environment interactions. | We measured plasma PAH-albumin adducts by competitive enzyme linked immune sorbent assay using monoclonal antibody 8E11 that recognises benzo(a)pyrene diolepoxide tetrols and related PAH metabolites. |
| 13 | **Lee KH**, Shu XO, Gao YT et al. Cancer Epidemiol Biomarkers Prev 19(3): 877–883. **2010.** | nested case-control study. In the Shanghai **China** | PAHs | Urinary | After diagnosis | 1997 - 2000 | No association was observed for PAH metabolites and the oxidative stress biomarkers of urinary malondialdehyde and 8-hydroxy-2'-deoxyguanosine and risk of breast cancer. | This nested case-control study provides no evidence of association between PAH exposure and oxidative stress and risk of breast cancer in Shanghai women. | Information on demographic characteristics, past medical history, lifestyles, history of menstruation, pregnancy history, eating and drinking habit, history of residence, family history. |

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| N° | Name of researchers / scientific journal | Place and study design | Exposure contaminants | Exposure assessment procedure | Time of sample collecting | Years of the Study interest | Exposure category or level / Risk estimate (95% CI) | Relevant Comment | Methods and possible covariates |
|---|---|---|---|---|---|---|---|---|---|
| 14 | **Saieva C,** Peluso M, Masala G, et al. Breast Cancer Res Treat. 129(2):477-84. **2011.** | Prospective EPIC- study. **Italy** | PAHs | Blood | Before and after diagnosis | 1993 - 1998 | Overall, no significant difference in DNA adduct levels emerged between cases and their matched controls | Conditional regression analyses adjusted for selected potential confounders did not show any significant association between DNA adduct levels and BC risk. Thus, our results provide no evidence that bulky DNA adducts measured in peripheral leukocytes are associated with BC risk. | Age, BMI, smoking habits, education level, age at menarche, age at first delivery, and alcohol consumption |

## ANNEX 4 – References Polycyclic Aromatic Hydrocarbons (PAH) monographs IARC, reviews, meta – analysis.

| | MONOGRAPHS IARC - PAHs | N° | REVIEWS - PAHs |
|---|---|---|---|
| 1 | **IARC Monographs. Some non-heterocyclic polycyclic aromatic hydrocarbons and some related exposures. Vol. 92: 1–853. 2010** | 1 | **Korsh J,** Shen A, Aliano K et al. **Breast Care. 10(5):316-8. 2015.** |
| 2 | **IARC Monographs. Bitumens and Bitumen Emissions, and Some N– and S-Heterocyclic Polycyclic Aromatic Hydrocarbons." Vol. 103. 2013** | | |

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## ANNEX 5 – References Perfluoroalkyl substances (PFASs, PFOS, PFOSA and PFOA) articles.

| N° | Name of researchers / scientific journal | Place and study design | Exposure contaminants | Exposure assessment procedure | Time of sample collecting | Years of the Study interest | Exposure category or level / Risk estimate (95% CI) | Relevant Comment | Methods and possible covariates |
|---|---|---|---|---|---|---|---|---|---|
| 1 | **Bonefeld-Jorgensen EC**, Long M, Bossi R, et al. **Environmental Health, 10:88,** 2011. | Case control study. **Greenland** | PFOA, PFOS | Blood Samples | After diagnosis | 2000 - 2003 | PFOS (ng/ml) OR = 1.03 (1.001; 1.07) *p = 0,05* | A case–control study of Greenland Inuit women found a positive statistically significant association between PFOS exposure and breast cancer but not statistically significant association between PFOA exposure and breast cancer. | Age, BMI, pregnancies, and cotinine; |
| 2 | **Ghisari M**, Eiberg H, Long M, et al. **Environ Health.** Mar 16;13(1):19. 2014. | Case–control study. Greenlandic Inuit women **North Canadian** | PFOA, PFOS | Blood Samples | After diagnosis | 2000 - 2003 | Furthermore, an increased BC risk was observed for women with high serum levels of perfluorooctane sulfonate (PFOS) and perfluorooctanoic acid (PFOA) | The BRCA1 founder mutation and polymorphisms in CYP1A1 (Val) and CYP17 (A1) can increase the BC risk among Inuit women and the risk increases with higher serum levels of PFOS and PFOA | Age, BMI, smoking, menopause status, information on serum levels of PFOA / PFOS. |
| 3 | **Bonefeld-Jorgensen EC**, Long M, Fredslund SO, Bet al. **Cancer Causes Control. 25(11):1439-48.** 2014. | Case-cohort study. **Denmark.** | PFOA, PFOS | Blood Samples | 15 years Before the diagnosis | 1996-2002 | PFOSA in the 5$^{th}$ quintile RR=2.40, 95% CI = 1.20, 4.83 | The results of this study suggest an association between BC and the measured PFOSA | Age, BMI, smoking, menopause status, information on serum levels of PFOA / PFOS. Questionnaires on lifestyle and environmental exposure (including diet, height, weight, diseases in the family, smoking, and alcohol intake) |

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| N° | Name of researchers / scientific journal | Place and study design | Exposure contaminants | Exposure assessment procedure | Time of sample collecting | Years of the Study interest | Exposure category or level / Risk estimate (95% CI) | Relevant Comment | Methods and possible covariates |
|---|---|---|---|---|---|---|---|---|---|
| 4 | **Barry V**, Winquist A, Steenland K. **Environ Health Perspect. 121(11-12):1313-8. 2013;** | Cohort Analysis. Mid-Ohio Valley. **USA** | PFOA | Serum | After diagnosis | 1992–2011 | Breast Cancr HR = 0.93 (0.88, 0.99) | The results of this study suggest no association between BC and the measured PFOA | Proportional hazards modelling, using time varying cumulative exposure, adjusting for time-varying smoking, time-varying alcohol use, sex, education, 5-yr birth period; |
| 5 | **Vieira VM,** Hoffman K, Shin HM, et al. **EHP**,**Vol. 121, number 3. 2013;** | A Geographic Analysis. Parkersburg, West Virginia and Ohio. **USA** | PFOA | Serum | Before diagnosis | 1996-2005 | Estimated serum levels PFOA (µg/L) 10 yr before diagnosis (breast incidence) Low: 3.7–12.8 RR (95% CI) 0.9 (0.7–1.2) Medium: 12.9–30.7 RR (95% CI) 1.1 (0.8–1.5) High: 30.8–109 RR (95% CI) 0.7 (0.5–1.0) Very high: > 110 RR (95% CI) 1.4 (0.9–2.3) No evidence breast cancer | Our results suggest that higher PFOA serum levels may be associated with testicular, kidney, prostate, and ovarian cancers and non-Hodgkin lymphoma but no breast cancer | Age, BMI, smoking, information on serum levels of PFOA. Using geocoding, we were able to identify cases living within a contaminated water district area. |
| 6 | **Wielsoe M,** Kern P, Bonefeld-Jørgensen EC.**Environmental Health 16:56, 2017;** | Case-control study of Inuit women. **Greenland.** | PFAAS / PFOA | Serum | After diagnosis | 2000-2003 and 2011-2014 | Odds ratio of breast cancer risk associated with serum levels of PFAAs (ng/ml serum) PFOA OR (95% CI) 1.26 (1.01; 1.58) 1.00 (reference) 2nd Tertile 1.86 (0.80; 4.31) 3rd Tertile 2.64 (1.17; 5.97) | Significant, positive associations between breast cancer risk and PFOA and PFAAs were observed. | Information about age, body mass index (BMI), smoking status, menopause status, number of full term pregnancies, and history of breastfeeding was obtained from questionnaires. |

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**ANNEX 5 – References Perfluoroalkyl substances (PFASs, PFOS, PFOSA and PFOA) monographs IARC, reviews, meta – analysis.**

| | MONOGRAPHS IARC - PFASs | N° | REVIEWS - PFASs |
|---|---|---|---|
| 1 | IARC Monographs. Vol. 110. 2010 | 1 | **Steenland K,** Fletcher T, Savitz DA. **Environ Health Perspect. Aug;118(8):1100-8. 2010.** |
| | | 2 | **Siddique S,** Kubwabo C, Harris SA. **Emerging Contaminants 2, 204-219. 2016.** |

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## ANNEX 6 – References Triazine (atrazine, simazine, terbuthylazine and metabolites desethyl-atrazine, desethyl-terbuthylazine) articles.

| N° | Name of researchers / scientific journal | Place and study design | Exposure contaminants | Exposure assessment procedure | Time of sample collecting | Years of the Study interest | Exposure category or level / Risk estimate (95% CI) | Relevant Comment | Methods and possible covariates |
|---|---|---|---|---|---|---|---|---|---|
| 1 | **Kettles MA**, M K Kettles, S R Browning, et al. **105(11): 1222–1227. Environ Health Perspect. 1997.** | An ecologic study. Kentucky. **USA** | **Triazine** | water contaminant, corn planted, and pesticide use variables, counties were categorized by exposure status. | / | 1991 - 1994 | There is a statistically significant increase in breast cancer risk with medium and high levels of triazine exposure [OR = 1.14 p<0.0001 and OR = 1.2 p<0.0001]. | The results suggest a relationship between female breast cancer incidence and triazine herbicide exposure. | Data on groundwater contamination. Data on surface water contamination. Survey of the amount of pesticide used by applicators in each county was examined |
| 2 | **McElroy JA**, Gangnon RE, Newcomb PA, et al. **J Expo Sci Environ Epidemiol, 2007.** | Case-control study. In rural areas in Wisconsin. **USA** | Atrazine | exposure estimation technique using a publicly available data set to examine atrazine exposure, in relation to breast cancer risk. | / | 1988-2001 | The possible risk for women exposed to levels of atrazine at or above statutory action levels of >3 ppb (OR 1.3, 95% CI 0.3–6.5) could not be ruled out due to small numbers in this category. | Resultsf rom this large population based study do not suggest an increased risk of breast cancer from adult exposure to atrazine in drinking water. | lifestyle risk factors: alcohol consumption and breast feeding habits; hormone replacement therapy use ; and finally, physical activity patterns.Analysiswasli mited to women who lived in rural areasof Wisconsin. |
| 3 | **Engel LS,** Hill DA, Hoppin JA, et al. Am J Epidemiol. 15;161(2):121-35. **2005.** | Cohort study. In Iowa and North Carolina**.** **USA** | Atrazine and other pesticides | Pesticide exposure and Breast Cancer Risk | / | 1993 - 1997 | Breast cancer standardized incidence ratios were 0.87 (95% C.I.: 0.74, 1.02) for women who reported ever applying pesticides and 1.05 (95% C.I.: 0.89, 1.24) for women who reported never applying pesticides. | The authors found no clear association of breast cancer risk with farm size or washing of clothes worn during pesticide application, but risk was modestly elevated among women whose homes were closest to areas of pesticide application. | Questionnaires directed to the farmers elicited similar but more detailed information on lifetime pesticide use, including the duration and frequency of use of specific pesticides. |

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| N° | Name of researchers / scientific journal | Place and study design | Exposure contaminants | Exposure assessment procedure | Time of sample collecting | Years of the Study interest | Exposure category or level / Risk estimate (95% CI) | Relevant Comment | Methods and possible covariates |
|---|---|---|---|---|---|---|---|---|---|
| 4 | **Rich CH**, Stump ML, Browning SR. **Arch Environ Contam Toxicol. Jan;42(1):127-36.2002.** | An ecologic study. Kentucky. **USA** | Atrazine | For this study, we assumed that the main route of atrazine exposure to the general population was through drinking water. | / | 1993 - 1997 | A null association was found for breast cancer across all exposure indices, both by county. | The results of this ecologic study did not generally support an association between exposure to the herbicide atrazine and breast cancer | An ecologic study was conducted using secondary data to derive measures of environmental exposure to atrazine in Kentucky |
| 5 | **Mills PK and Yang R. J Environ Health.68(6):15-22; 2006;** | Regression analysis California Latinas. **USA** | Triazine and other pesticides | Exposure at two classes of pesticides, organochlorines and triazine herbicides | / | 1988-2000 | No significant associations were found for the triazine herbicides atrazine and simazine. | Risk of breast cancer was inversely and significantly associated with fertility levels. | Age, socioeconomic status, and fertility rates. |
| 6 | **Hopenhayn-Rich C,** Stump ML, Browning SR.**Arch Environ Contam Toxicol 42:127–136. 2002;** | An ecologic study. Kentucky. **USA** | Atrazine | exposure to atrazine and the association between these measures and incidence of breast cancer | / | 1993 - 1997 | The ORs were 1.01 (95% CI 0.96, 1.05) and 0.98 (95% CI 0.93, 1.02) for the highest and next to- highest atrazine exposure groups, respectively. | A null association was found for breast cancer across all exposure indices. | The results of this ecologic study did not generally support an association between exposure to the herbicide atrazine and breast cancer |
| 7 | **Muir K,** Rattanamongkolgul S, Smallman-Raynor M, et al. **Public Health. 118(7):513-20. 2004;** | The ecological study. **UK** | Atrazine and other pesticides | breast cancer and environmental exposure to pesticides and the geographical distribution of pesticides | / | 1989 - 1991 | The ecologic studies do not support a causal relationship between breast cancer and atrazine. | Although pesticides do vary significantly in their spatial application, overall, consistent associations between breast cancer incidence rates and the pesticides applied were not found. | Information relating to all cases of female breast cancer (age .45 years at diagnosis), resident and diagnosed in Lincolnshire and Leicestershire in the period 1989–1991. |
| 8 | **Beane Freeman LE,** Rusiecki JA, Hoppin JA. **Environ Health Persp 119: 1253–1259. 2011;** | Cohort Study. Iowa and North Carolina. **USA** | Atrazine | Breast cancer incidence and its possible spatial association and exposure with pesticide application in two counties of England | / | 1994 - 2007 | there was no consistent evidence of an association between atrazine use and breast cancer. | In conclusion, despite high incidence of breast cancer in Lincolnshire and Leicestershire, the findings do not show localized spatial distribution of breast cancer incidence within these counties. | Information relating to all cases of female breast cancer, age (>45y), resident and diagnosed, pesticide application, |

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**ANNEX 6 – References Triazine (atrazine, simazine, terbuthylazine and metabolites desethyl-atrazine, desethyl-terbuthylazine) monographs IARC, reviews, meta – analysis.**

| | MONOGRAPHS IARC - Triazine | N° | REVIEWS - Triazine |
|---|---|---|---|
| 1 | IARC Monographs. Vol. 73. 1999 | 1 | Boffetta P, Eur J Cancer Prev, 2013; |
| | | 2 | Simpkins JW, Swenberg JA, Weiss N, et al. Toxicol Sci. Oct;123(2):441-59. 2011. |
| | | 3 | Sathiakumar, N., MacLennan, P. A., Mandel, J. Et al. Crit. Reviews Toxicol. 41(Suppl. 1), 1–34. 2011. |

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## ANNEX 7 – References Cadmium (Cd) articles.

| N° | Name of researchers / scientific journal | Place and study design | Exposure contaminants | Exposure assessment procedure | Time of sample collecting | Years of the Study interest | Exposure category or level / Risk estimate (95% CI) | Relevant Comment | Methods and possible covariates |
|---|---|---|---|---|---|---|---|---|---|
| 1 | **Pan J**, Environ Geochem Health, **2010;** | Ecological study. **Europe** | Cadmium | European Geological Surveys geochemical baseline data to examine the distribution of cadmium (Cd) in Europe, with a particular reference to the international soil and water guideline values. | / | 2010 | The geochemical data used in this study were from the new Forum of European Geological Surveys (FOREGS), whereas the data on cancer incidence were from the International Agency for Research on Cancer (IARC) GLOBOCAN 2002 database. | In terms of human health impacts, food (up to several hundred lg/day) was found as the only major route of exposure to Cd for the non-smoking general population. | In this study, the incidence data on breast cancer for 26 European countries were used. In this study, the human health-related pathways of Cd were hence reviewed first |
| 2 | **Gallagher CM**, Research Paper, **2010;** | case-control study. **Long Island. USA** | urinary cadmium (UCd), | urine and blood samples | / | 1999-2008 | women in the highest quartile had increased risk for breast cancer (OR=2.69; 95% CI=1.07, 6.78) and US women in the two highest quartiles had increased risk (OR=2.50; 95% CI=1.11, 5.63 and OR=2.22; 95% CI=.89, 5.52, respectively). | Further research is warranted on the impact of environmental cadmium on breast cancer risk in specific populations and on identifying the underlying molecular mechanisms. | health questionnaire including family history of breast cancer, use of hormone therapy other than birth control pills, age at first live birth, and menopausal status, provided a blood sample. |

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| N° | Name of researchers / scientific journal | Place and study design | Exposure contaminants | Exposure assessment procedure | Time of sample collecting | Years of the Study interest | RR (95% CI) | Relevant Comment | Methods and possible covariates |
|---|---|---|---|---|---|---|---|---|---|
| 3 | **McElroy JA**, Shafer MM, Trentham-Dietz A, **J Natl Cancer Inst. 2006;** | case-control study. Wisconsin. **USA** | urinary cadmium (UCd), | urine samples | / | 2004-2005 | Women in the highest quartile of creatinine-adjusted cadmium level ( ≥ 0.58 µg/g) had twice the breast cancer risk of those in the lowest quartile (<0.26 µg/g; OR = 2.29, 95% CI = 1.3 to 4.2) | there was a statistically significant increase in risk with increasing cadmium level. | All participants were interviewed about physical activity, reproductive history, alcohol consumption, height and weight, use of oral contraceptives and hormone replacement therapy, personal and family medical history, demographic factors, a limited set of dietary components, and smoking history. |
| 4 | **Nagata C**, Nagao Y, Nakamura K. **Breast Cancer Res Treat. 2013;** | case-control study. **Japan** | urinary cadmium level | urine samples | after diagnosis (19 days) | 2000-2002 | Women in the highest tertile of the creatinine adjusted cadmium level ([2.620 lg/g) had significantly elevated OR of breast cancer relative to those in the lowest tertile (1.674 lg/g) after controlling for covariates OR = 6.05, (95 % CI 2.90, 12.62 | We found that a higher urinary cadmium level was associated with an increased risk of breast cancer among Japanese women. | Age, BMI, menopausal status, and year of urine sampling, smoking and drinking habits, diet, physical activity, use of medication, medical history, and reproductive history |

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| N° | Name of researchers / scientific journal | Place and study design | Exposure contaminants | Exposure assessment procedure | Time of sample collecting | Years of the Study interest | RR (95% CI) | Relevant Comment | Methods and possible covariates |
|---|---|---|---|---|---|---|---|---|---|
| 5 | **Strumylaite L**, Bogusevicius A, Abdrachmanovas O, et al. **Breast Cancer Res Treat. 2011;** | Study of (Cd) concentration in different biological media. **Lithuania** | cadmium (Cd) | breast adipose tissue, urine, and blood | after diagnosis | 2007 | Cd in urine was significantly higher in cancer patients than in controls (P < 0.001). | Cancer patients with positive estrogen receptors (ERs) had significantly greater concentration of breast tissue Cd compared to patients with negative ERs (P = 0.035). | Questionnaire demographic characteristics and smoking. The ER and progesterone-receptor (PR) levels were measured in the specimens of breast tissue from breast cancer |
| 6 | **Antila E,** Mussalo-Rauhamaa H, Kantola M, Atroshi F, Westermarck T. **Sci Total Environ 186:251-256. 1996;** | Case control study. **Finnish** | Association of cadmium with human breast cancer. | breast adipose tissue | after diagnosis | / | The cadmium concentrations found in the breast cancer patients did not differ statistically significantly from those of the healthy control | The postmenopausal breast cancer, decline in progesterone levels, and increased Cdtoxicity may be causally related. | In a questionnaire recording age, height, weight, smoking, fish-eating habits, parity, and previous breast-feeding. |

## ANNEX 7 – References Cadmium (Cd) monographs IARC, reviews, meta – analysis.

| | MONOGRAPHS IARC - Cadmium | N° | REVIEWS - Cadmium |
|---|---|---|---|
| 1 | **IARC Monographs. Vol. 58. 1993** | 1 | **Jarup L, Berglund M, Elinder CG, et al. Scand J Work Environ Health 24(suppl 1):1–52. 1998.** |

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## ANNEX 8 – References Trihalomethanes articles.

| N° | Name of researchers / scientific journal | Place and study design | Exposure contaminants | Exposure assessment procedure | Time of sample collecting | Years of the Study interest | RR (95% CI) | Relevant Comment | Methods and possible covariates |
|---|---|---|---|---|---|---|---|---|---|
| 1 | **Doyle TJ,** Zheng W, Cerhan JR,et al.. **Am J Public Health. Jul;87(7):1168-76.1997;** | A Prospective Cohort Study. Iowa**. USA** | trihalomethanes | An association between breast cancer risk and exposure of chlorination | / | 1986 - 1993 | An excess risk of breast cancer (RR = 1.33, 95% CI = 1.02, 1.74) was also observed in relation to surface water use. | Measurements of four trihalomethanes were performed on 252 municipal water supplies in Iowa. | Age, BMI, medical history, anthropometric data, and information concerning diet and risk factors for cancer, the types of drinking water. |
| 2 | **Koivusalo M,** Pukkala E, Vartiainen T, et al.**Cancer Cause Control. 8:192 – 200.1997;** | Cohort study **Finland.** | trihalomethanes | Drinking water chlorination and cancer-a historical cohort study in Finland. | / | 1971 - 1993 | RR an average exposure in a town using chlorinated surface level compared with those not exposed to chlorinated surface water. After adjustment for confounding, a statistically significant excess risk was observed for women in cancer of breast (RR = 1.11, CI = 1.01-1.22). | The increased risks were found primarily for women. | age, time period, urbanization, gender, and social-status |
| 3 | **Vinceti M,** Fantuzzi G, Monici L, et al. **Sci Total Environ. Sep 1; 330(1-3):47-53.2004;** | A retrospective cohort study in northern **Italy** | trihalomethanes | trihalomethane exposure through drinking water and cancer mortality in northern Italy | / | 1987 - 1999 | The risk of breast and ovarian cancer and of prostate cancer also tends to increase in subjects with higher socio–economic status, so the excess rates detected in our exposed cohort cannot be easily ascribed to life-style confounders. | There is epidemiologic evidence indicating that a higher socioeconomic status is directly associated with risk of breast cancer. | we also extracted all available information concerning the occupational status and educational attainment levels of this population at that date. |

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| N° | Name of researchers / scientific journal | Place and study design | Exposure contaminants | Exposure assessment procedure | Time of sample collecting | Years of the Study interest | RR (95% CI) | Relevant Comment | Methods and possible covariates |
|---|---|---|---|---|---|---|---|---|---|
| 4 | **Ribera LF**, Lavedan EG, Aragonés N. et al. **Environment International 112;227–234.2018;** | multicase-control study **Spanish** | trihalomethanes, chloroform | Long-term exposure to trihalomethanes in drinking water and breast cancer in the Spanish multicase - control study on cancer | / | 2008 - 2013 | Adult-lifetime residential chloroform was associated with BC (adjusted OR =1.47; 95%CI =1.05, 2.06 for the highest (> 24 µg/L) vs. lowest (< 8 µg/L) quartile; p-trend =0.024) | At common levels in Europe, long-term residential total THMs were not related to female breast cancer. A moderate association with chloroform was suggested at the highest exposure category. | Age, residential history, water source in each residence (bottled, tap, other) and frequency and duration of bathing, educational level, occupational status, race, BMI, family history of BC, menopausal status, oral contraceptive use, age at menarche. |
| 5 | **Marcus PM,** Savitz DA, Millikan RC et al. **Epidemiology Vol. 9, No. 2, Mar., 1998;** | Ecological study. North Carolina. **USA** | trihalomethanes | Female breast cancer and exposure to trihalomethane levels in drinking water in North Carolina. | / | 1995 - 1997 | total trihalomethane category was not very different in black women (rate ratio = 1.2; 95% CI = 0.8-1.8) than in white women (rate ratio = 1.1; 95% CI = 0.9-1.3). | Total trihalomethane levels were not associated materially with breast cancer risk, adjusting for potential confounders. | ecologic measurements of age, income, education, urban status, and race as potential confounders. |

## ANNEX 8 – References Trihalomethanes monographs IARC, reviews, meta – analysis.

| | MONOGRAPHS IARC - Trihalomethanes | N° | REVIEWS - Trihalomethanes |
|---|---|---|---|
| 1 | **IARC Monographs. Vol. 101. 2013** | 1 | **Mohamadshafiee MR, Taghavi L. World Academy of Science, Engineering and Technology International Journal of Environmental and Ecological Engineering Vol:6, No:8, 2012.** |
| 2 | **IARC Monographs. Vol. 52. 1991** | | |

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