WASABY

WASABY

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

D7.1 Literature review on the main persistent environmental contaminants related to breast cancer

WP7 – Borgini Alessandro

V1 – 31st March 2019

Co-funded by the Health Programme of the European Union

EU funding disclaimer: This project has received funding from the 3rd European Union Health Programme 201-2020 under Grant Agreement PP-2-5-2016 (# 769767)

WASABY European Project - WP7 Report

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

TABLE OF CONTENTS

1. Introduction and general objective of WP7 3
2. Methods and means 3
3. Environmental contaminants considered 4
   - 3.1. Polychlorinated biphenyls (PCBs) 6
   - 3.2. Dichlorodiphenyltrichloroethane (DDT) and its metabolites (DDD, DDE) and others organochlorine compounds (Lindane, Hexachlorobenzene (HCB), Chlordane, ecc.) 15
   - 3.3. Dioxin (TCDD) 23
   - 3.4.Polycyclic Aromatic Hydrocarbons (PAH) 28
   - 3.5. Perfluoroalkyl substances (PFASs, PFOS, PFOSA and PFOA) 33
   - 3.6. Triazine (atrazine, simazine, terbuthylazine and metabolites desethyl-atrazine, desethyl-terbuthylazine) 37
   - 3.7 – Cadmium (heavy metal) 42
   - 3.8 – Trihalomethanes (THMs) (bromoform, bromo-dichloro-methane, dibromochloromethane, chloroform) 46
4. General conclusion 49

Co-funded by the Health Programme of the European Union

EU funding disclaimer: This project has received funding from the 3rd European Union Health Programme 201-2020 under Grant Agreement PP-2-5-2016 (# 769767)

1. Introduction and general objective of WP7

The WASABY project concerns the design of a model able to identify areas with higher cancer rates, in order to study whether the contamination of the most persistent pollutants in soil and in deep water can cause an increase in the risk of breast cancer. One of the main objectives of WP7 is to analyze the relationship between environmental data and the incidence of breast cancer following the following aim: identify, through a **scientific literature** review, persistent contaminants in the aqueous matrix (especially in deep waters) and in the soil matrix, , assessing environmental risk factors and exposure to contaminants, in relation to breast cancer. Several scientific articles were found to correlate exposure to persistent environmental contaminants, mainly, but not only, with POPs (Persistent Organic Pollutants), present in the two environmental matrices (water and soil) and the risk of breast cancer for women.

2. Methods and means

When we searched scientific articles correlating exposure to Persistent Organic Pollutants (POPs) and the risk of having breast cancer for women, we considered and selected the most important articles of population studies (e.g., case-control and cohort studies) starting from scientific reviews, meta-analysis and IARC monographs on POPs exposure through biological matrices before or after breast cancer diagnosis (e.g., blood samples, plasma and breast tissue) . In our literature research, we included ‘‘breast cancer’’ in combination with environmental pollutant; criteria include original studies published in a peer-reviewed journal with a case-control, nested case-control or cohort design, estimating breast cancer risk (odds ratio, risk ratio or hazard ratio) associated with environmental exposure to combustion products, pesticide, drinking water, organic solvent, heavy metals (cadmium, lead, nickel, etc.), polychlorinated biphenyl (PCBs), organochlorine pesticides, DDT,p,p’; DDT,o,p’; DDD,p,p’; DDE,p,p’; Hexachlorobenzene (HCB), Dieldrin, Alachlor, polycyclic aromatic hydrocarbon (PAH), triazine and metabolites, Perfluoroalkylated substances (PFAS), cadmium (heavy metal), and trihalomethanes (THMs) (bromoform, bromo-dichloro-methane, dibromochloromethane, chloroform). In our search, we also incorporated ‘‘breast cancer’’ and each of the chemicals identified as a mammary carcinogen. We limited inclusion to articles published from the late 90s to the present day, for all contaminants, because there are different useful reviews covering earlier articles and we sought to update these reviews, minimizing redundancy. Articles were reviewed to identify and evaluate inclusion criteria for study participants, comparability of control or reference groups, exposure measurement method, control for confounding, and the strength of observed associations. All studies included are controlled for age and sex, and are all restricted to females. A critical review for each study was entered in a database. Results were summarized in tables for the most-studied exposure sources in Annex 1-8.

Co-funded by the Health Programme of the European Union

EU funding disclaimer: This project has received funding from the 3rd European Union Health Programme 201-2020 under Grant Agreement PP-2-5-2016 (# 769767)

3. Environmental contaminants considered

In this part of the WP7 we set out to review and synthesize epidemiologic evidence concerning breast cancer and environmental pollutants identified as mammary carcinogens or endocrine disrupting compounds, including: persistent organochlorine pollutants (POPs) and other contaminants routinely monitored by the environmental agencies of Europe in the various environmental water and soil matrices, and included in specific standardized databases.

They are environmentally persistent and lipophilic. They are frequently detected in food, soil, and dust, concentrate up the food chain, and are found in human breast milk and adipose tissue. Residues can be readily measured in blood and breast tissue, providing a way to quantify exposure, although these measures are invasive and expensive; therefore, as a practical matter, levels cannot be measured repeatedly in an individual. They include:

3.1 Polychlorinated biphenyls (PCBs). PCBs are a group of man-made organic chemicals consisting of carbon, hydrogen and chlorine atoms.

3.2 Dichlorodiphenyltrichloroethane (DDT) and its metabolites (DDD, DDE) and others organochlorine compounds as 1,1-Dichloro-2,2-bis(4-chlorophenyl)ethene (DDE) and dichlorodiphenyldichloroethane (DDD) and pesticides like Dieldrin, hexachlorobenzene (HCB), Hexachlorocyclohexane, Chlordane.

3.3 Dioxins are unwanted by products of chemical processes that contain chlorine and hydrocarbons. There are at least 100 different kinds of dioxins such as 2,3,7,8-tetrachlorodibenzo-pdioxin (TCDD).

Others pollutants

3.4 Polycyclic aromatic hydrocarbons (PAHs). Ubiquitous group of several hundred chemically-related, environmentally persistent organic compounds of various structures and varied toxicity

3.5 Perfluoroalkylated substances (PFAs). A large group of man-made chemicals. PFAS include

- perfluoro carboxylated acids (PFCAs) perfluorosulfonated acids (PFSAs), which include
- perfluorooctanoic acid (PFOA) and perfluorooctane sulfonate (PFOS)

3.6 Triazine group of chemicals are most widely used herbicides in the world. This group consists of atrazine, simazine, propazine and cyanazine.

3.7 Heavy metals. In principle Cadmium can play an important role in the risk of breast cancer

3.8 Trialomethanes. Trihalomethanes (THMs) are halogen-substituted single-carbon compounds most commonly present in drinking-water are chloroform (CHCl3), bromodichloromethane or dichlorobromomethane (CHBrCl2) (BDCM), dibromochloromethane or chloro-dibromomethane (CHClBr2) (DBCM), and bromoform (CHBr3).

Co-funded by the Health Programme of the European Union

EU funding disclaimer: This project has received funding from the 3rd European Union Health Programme 201-2020 under Grant Agreement PP-2-5-2016 (# 769767)

The following chapters of the Report are all structured in the same way:
In the **Contaminants considered**, we list the main properties of the family of contaminants considered, from the molecular structure, to the chemical-physical properties, to the persistence in the environment and to the main contamination in the various environmental matrices, especially in water and soil.

In the **Source,** the main sources of anthropogenic emissions of the contaminants are considered in the various environmental matrices (air, water, soil, sediments and biota) and the main use.

In the **Mean of exposure,** the different modalities of exposure of the contaminants considered towards the man are evaluated, passing for example through the trophic chain, the contact, the respiration also evaluating the potential toxic effects of the contaminants.

In the **Regulation and/or persistence,** the various directives and laws that regulate the use of the contaminants considered are evaluated.

In the **Evidence on (breast) cancer risk**, scientific studies of population (case control / cohort) are presented where a correlation was found between the different persistent contaminants considered and breast cancer.

In the **IARC Monography**, the most important scientific studies on the population that assessed the exposure to the considered persistent contaminants (also family of contaminants) and the correlation with the breast cancer are often analyzed through a biological sampling of women cases and controls considered (blood samples and breast tissue).

In the **Reviews and meta-analyses,** we analyzed the main reviews and meta-analyses in literature that covered the exposure to the considered persistent contaminants in correlation with breast cancer.

In the **ANNEX,** results are summarized as **Annexes 1-8** in form of tables for the main classes of persistent contaminants. The tables all have the same approach: the name of the first three researchers of the scientific paper; the design of the observational study (case-control, cohort, etc.); the geographic location; exposure to the main persistent contaminants; the years of interest of the study; the relative risk observed; the main comments relevant to the scientific article; the possible covariates and methods used.

Co-funded by the Health Programme of the European Union

EU funding disclaimer: This project has received funding from the 3rd European Union Health Programme 201-2020 under Grant Agreement PP-2-5-2016 (# 769767)

3.1. Polychlorinated biphenyls (PCBs)

Contaminants considered

PCBs are a class of organic compounds with one to ten chlorine atoms attached to a biphenyl, which is a molecule composed of two benzene rings. Polychlorinated biphenyls (PCBs) represent a class of 209 congeners, classified based on the number and relative position of the chlorine atoms on the biphenyls. PCBs are highly persistent in the environment and today vast areas near former production sites are still polluted. PCBs contamination results particularly alarming when impacting agricultural soil, since they effectively enter the food chain. PCBs concentrate in soil and sediment but can also adsorb to small organic and mineral particles, therefore traveling far from the initial contamination site, carried by wind and water. Because they are so persistent and lipophilic, PCBs tend to accumulate in animals and human tissues.

Source

PCBs are industrial chemicals that have been used for various commercial applications such as hydraulic fluids, printing inks or capacitor dielectric liquids. Transformers probably represent the largest source of PCB and are easily identifiable since their nameplates indicate that they are insulated with PCB dielectric. Other PCB applications include plasticizers in paints and cements, stabilizing additives in flexible PVC coatings of electrical cables and electronic components, pesticides extenders, cutting oils and lubricants, flame retardants, such as adhesives, wood floor finishes, paints, in de-dusting agents, in waterproofing compounds.

Mean of exposure

Once in the environment, the PCBs enter the food chain: most of human exposure to PCB is through food. Such exposure also has neurotoxic and immunotoxic effects. In addition, PCB undergo long-range transport through air, water and migratory species. They travel across international boundaries and are deposited far from their point of release, and accumulate in terrestrial and aquatic ecosystems. There is therefore an urgent need for PCB to be inventoried, taken out of use and managed in an environmentally sound manner. Adults are mainly exposed through the consumption of dairy products, meat and fish. PCBs exist in 12 of these 209 molecules (which are coplanar) are characterized by a toxicity compared to that of dioxins and are defined dioxine-like PCBs. These have serious effects on human's health, such as immune and endocrine system disruption, interference with fetal development, acute and chronic toxicity, carcinogenicity.

Co-funded by the Health Programme of the European Union

EU funding disclaimer: This project has received funding from the 3rd European Union Health Programme 201-2020 under Grant Agreement PP-2-5-2016 (# 769767)

Regulation and/or persistence

The directive 96/59/EC establishes the requirements for an environmentally friendly disposal of PCBs, aiming to dispose of all PCBs contained in them; in addition, Member States must take an inventory of large equipment containing PCBs, must adopt a plan for the disposal of inventoried equipment and lines for the collection and disposal of non-inventoried equipment (small electrical equipment very often found in appliances manufactured before the ban on marketing of PCBs).

Experience in many developing countries has shown that the lack of an adequate regulatory framework on the PCB can seriously hamper the inventory process. In many cases, roles and responsibilities are not clear, which means that no institution is responsible for regulating and monitoring the use of PCBs.

Evidence on (breast) cancer risk

Studies on workers' PCBs have shown that they can be associated with certain types of cancer in humans, such as liver and biliary cancer. As a result, the International Agency for Research on Cancer IARC has classified the PCB as a "human carcinogen" group 1. Regarding the Evidence on (breast) cancer risk on the exposure of PCBs there are several studies of population well studied by the recent IARC Monograph (year 2016) on PCBs, and also in several reviews and meta-analyzes of scientific literature.

Different case-control studies do not find a statistically significant relationship between exposure to PCBs (through blood samples and adipose tissue analisys) and breast cancer, but some articles, confirmed in the 2016 IARC Monograph and in the most recent reviews of scientific literature and meta-analysis, find a statistically significant association between exposure to some PCBs congeners and breast cancer.

For example, in the hospital-based case-control study conducted in 1994-1996 in Mexico City **[Lopez-Carrillo 1997],** 141 cases aged between 20 and 79 years from participating hospitals and an equal number of controls without cancer were enrolled. Serum levels of PCBs were analysed in 95 histologically confirmed breast cancer cases and 95 hospital controls, 2079 years of age. After adjusting for established risk factors, there was no evidence of a relationship between PCBs and breast cancer risk (OR=1.31, 95% CI 0.33‑5.21) for the high category of exposure. This study lends no support to the case for a role for PCBs in breast cancer aetiology.

A recent case-control study carried out in Alaska **[Holmes 2014]** analyzed blood and adipose tissues collected after the diagnosis of breast cancer; also in this case they did not observe a significant association between some PCB congeners (PCB 138, 158, 153, 180) with risk of breast cancer.

Co-funded by the Health Programme of the European Union

EU funding disclaimer: This project has received funding from the 3rd European Union Health Programme 201-2020 under Grant Agreement PP-2-5-2016 (# 769767)

The purpose of a case-control study **in Spain [Lucena 2001]** was to examine the possible relationship between different PCBs congeners and breast carcinomas. In this study all the women treated with excision biopsy due to the lump were included, a questionnaire was performed for all the cases and controls, the body mass index was computed, a histopathological examination of the mass removed and the concentration of PCB levels in breast fat was calculated through samples of adipose tissue of which 48.5% were from women with benign lesions and 51.5% with malignant lesions. In multivariate analysis, the PCB-28 congener was found to be the most important risk factor (OR=9.6, 95% CI 3.8-24.4). The variables associated with the malignant lesions in the univariate analysis were age, lactation period, overweight, n-28 PCB and other PCB congeners. Other risk factors have been identified as age, alcohol, low parity and overweight.

A case-control study done in **Tunisia [Arrebola 2015]** finds an association (again from the blood samples analyzed after diagnosis) between the two PCB congeners (PCB138 and 180) in 69 cases of breast cancer and 56 controls. PCB138 and PCB180 were positively associated with breast cancer risk but only in univariate analysis.

In another recent case-control study **[Wielsoe 2017]** the Greenland inuit women were recruited in the period 2000-2003 and in the period 2011-2014. The diagnosis of breast cancer was confirmed by the histology. They found weak but positive associations between high serum concentrations (average/maximum vs. lower tertile) on the individual congeners of the more lipophilic PCBs (PCB99, PCB138, PCB153, PCB170, PCB170 and PCB183) and on the total PCBs there is an association with the risk of breast cancer.

IARC Monography

The International Agency for Research on Cancer (IARC) in the Monograph on the evaluation of carcinogenic risk to humans “Polychlorinated Biphenyls and Polybrominated Biphenyls” Vol. 107 (2016) **[IARC 2016]** classified PCBs as carcinogenic to humans based on evidence of malignant melanoma and positive associations with breast cancer and non-Hodgkin lymphoma. Some congeners PCB-118 and PCB-126 and highly chlorinated commercial mixtures (Araclor 1260, Araclor 1254, and Kanechlor 500) exhibit dioxin-like activity and bind to the aryl hydrocarbon receptor (AhR).

IARC’s evaluation of the carcinogenicity and exposure of PCBs and breast cancer was considered in many scientific articles.

The relationship between serum concentration of PCBs and breast cancer has been evaluated in different case‑control studies.

In the first five USA case control studies that we have analyzed, we have found a statistically significant relationship between some PCBs congeners and breast cancer.

Co-funded by the Health Programme of the European Union

EU funding disclaimer: This project has received funding from the 3rd European Union Health Programme 201-2020 under Grant Agreement PP-2-5-2016 (# 769767)

In a case-control study performed in New York **[Moysich 1998]**, 154 women with postmenopausal incidental breast cancer and 192 controls of the same age were compared by performing blood test samples, detecting specific chemical analyzes by serum concentrations of 73 PCBs congeners. No association between total PCBs exposure was found, but an increased risk was evident for the less chlorinated PCBs (OR=1.66, 95% CI 1.07-2.88 for the second and third tertile) among Parisian women who had never breast-fed; the magnitude of the risk was higher in 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).

In a case-control study conducted between 1993 and 1996 in North Carolina, USA, **[Millikan 2000]** breast cancer cases (778) and controls (659) among African American and white women were classified by age, race, menopausal status, BMI, breastfeeding, therapy hormone associated replacement and income. Total PCBs concentrations in plasma lipids were measured. The risk was particularly high for African American women with BMI>34.2 (total third of tertiary PCBs, OR=4.92, 95% CI 1.63-14.83); there was no risk among white women.

In another case-control study in Connecticut, USA **[Falck 1992]** mean concentrations of PCBs in the breast tissue of 20 women with breast cancer were significantly higher (p=0.02) than in 20 women with benign breast disease, and the association persisted after controlling for age, smoking, and BMI. There was approximately 1% increased risk for every 10 ppb of PCBs in adipose tissue.

In a case-control study in Connecticut, USA **[Holford 2000]** calculated the risk of breast cancer in relation to increases in exposure to 10 ng/g at different PCBs congeners. The researchers found that the PCB-180 and the PCB-183 congeners were associated with a statistically significant increase in breast cancer risk, for example for PCB-183 (OR=1.82, 95% CI 1.12-2.98).

An interesting case-control study that included primarily young women (premenopausal women) in Oakland, California [**Cohn 2012]** compared serum concentrations of 16 PCBs in serum samples stored at the beginning of postpartum collected between 1959 and 1967 by 112 breast cancer cases and 112 age-matched checks. The median time from blood sampling to diagnosis was 17 years and the average age at diagnosis was 43 years. No association between breast cancer risk and total PCB counts was reported, but for the PCB-203 congener a statistically significant association was found with an increased risk (OR=6.3, 95% CI 1.9-21.7) for the highest compared to the lower quartile.

Co-funded by the Health Programme of the European Union

EU funding disclaimer: This project has received funding from the 3rd European Union Health Programme 201-2020 under Grant Agreement PP-2-5-2016 (# 769767)

Also in a case–control study conducted in 1994–1997 in Quebec City, Canada **[Demers 2002]**, plasma concentrations of fourteen PCBs congeners were measured in 314 women with cancer of the breast and 523 controls (219 hospital controls, 304 population controls). The results suggest that exposure to dioxin-like PCBs increases breast cancer risk, specially associated with a total concentration of the three mono-ortho-substituted congeners of PCBs 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).

In another case-control study in Mexico **[Recio-Vega 2011]** 70 breast cancer cases were compared with 70 hospital controls by taking blood samples to measure 20 PCBs congeners. An increased risk of breast cancer was evident for total PCB (OR=1.09, 95% CI 1.02-1.16) and for exposure groups 2b (OR=1.90, 95% CI 1.25-2.88) and group 3 (OR=1.81, 95% CI 1.08-3.04) and group 4 (OR=1.57, 95% CI 1.20-2.07), defined according to the PCBs classification of **[Wolff 1995]**.

In a large case-control study on the population of environmental exposures to PCBs and breast cancer conducted in 1996-1997 in Long Island, NY, USA, **[Gammon 2002]** serum concentrations of 24 congeners PCBs were measured for 646 cases and 429 controls, with results presented for the four most common congeners (PCB-118, PCB-138, PCB-153 and PCB-180). There was no association between breast cancer and the concentration of the sum of the four PCBs; no effect of lactation, state of menopause, stage of disease or hormone receptor status.

In northern Europe, several case-control studies on breast cancer and exposure to PCBs, always measured by blood tests and/or through adipose tissue, have been conducted, for example in Sweden **[Liljegren 1998]**. The concentrations of PCBs were measured in mammary adipose tissue of 43 women with breast cancer and 35 controls. Equity-adjusted odds ratios for age and parity did not show any association with total PCBs congeners in all subjects.
In the Copenhagen City Heart Study (Denmark) **[Hoyer 1998]** a nested case-control study was conducted. Serum samples were obtained in 1976 from a cohort of 7712 women aged 20 years or older: after excluding subjects without a valid serum sample, 240 cases and 447 controls were included in the study. Concentrations of 28 PCBs congeners were detected in serum. No association between the risk of breast cancer and the correct lipid concentrations of the sum of PCBs or specific congeners has been reported.

Co-funded by the Health Programme of the European Union

EU funding disclaimer: This project has received funding from the 3rd European Union Health Programme 201-2020 under Grant Agreement PP-2-5-2016 (# 769767)

Five years later, the same subjects in the study performed a second serum sample **[Hoyer 2000]**. The analyses were conducted in this group for four congeners of common PCBs. A statistically significant risk was found for subjects in the highest quartile of the PCB congener concentration 138 (OR=2.1, 95% CI 1.0-4.4) while for total PCBs (OR=1.6) and for the congeners PCB-118 (OR=1.9) and PCB-153 (OR=1.3) the association was not significant.
Within the same cohort **[Hoyer 2001]** the overall survival of breast cancer in relation to serum organochlorine concentrations based on the state of estrogen receptors was evaluated. In general, the risk of dying among women with the highest organochlorine exposure level was higher among women with ERP than ERN breast cancers, but the only statistical significant relationship was observed for ΣPCB (RR=2.5, I vs. IV quartile, 95% CI 1.1-5.7), but not dose-response relation was apparent.
Two case-control studies were conducted in Belgium [**Charlier 2003 and 2004]**: in the first study, on 100 cases of breast cancer and 100 surgical controls, the concentrations of PCB-101 and PCB-153 congeners were significantly higher for cases compared to controls; in the second study on 60 cases and 60 controls, an association was reported only for the congener PCB-153 (OR=1.8, 95% CI 1.4-2.5) after adjustment for age and reproductive risk factors .

Also other case-control studies conducted in USA **[Krieger 1994; Dorgan 1999; Helzlsouer 1999; Wolff 2000; Laden 2001; Zhang 2004; Rubin 2006; Gatto 2007]**, in Canada **[Demers 2000]**, in Norway **[Ward 2000]** and in Japan **[Itoh 2009]** found no association between serum PCBs levels and breast cancer risk.

Different case-control studies were conducted on the relationship between the concentration of PCBs in adipose tissue and the risk of breast cancer in the USA **[Zheng 2000a and 2000b; Rusiecki 2004]**, in Denmark [**Raaschou-Nielsen 2005]** and these found no association between adipose tissue PCBs levels and breast cancer risk.
On the contrary, other large case-control studies that have related exposure to total or to different congeners PCBs through the analyzes of adipose tissue in women have found a statistically significant risk with breast cancer.

For example in the case-control study performed by **[Stellman 2000]** in Long Island, New York, USA, concentrations of 14 PCBs congeners in adipose tissue were analyzed in several women with breast cancer and several hospital controls adjusted by age, race and BMI. For PCB-156 and PCB-183 congeners, a significantly higher risk was found (OR=1.9, 95% CI 1.1-3.0) for the second exposure distribution tertile for PCB-156; and an OR=2.0 (95% CI 1.2-3.4) for the highest tertile of PCB-183.

Co-funded by the Health Programme of the European Union

EU funding disclaimer: This project has received funding from the 3rd European Union Health Programme 201-2020 under Grant Agreement PP-2-5-2016 (# 769767)

In another case-control study in Kingston and Toronto, Ontario, Canada, **[Aronson 2000]** non-cancerous breast fat tissue collected before treatment from 217 breast cancer incident cases and 213 biopsy controls was analyzed for 14 PCB congeners. A statistically significant association was found with breast cancer risk for PCB-105 (OR=3.17, 95% CI 1.51-6.68) and for PCB-118 (OR=2.31, 95% CI 1.11-4.78), with the fourth against the first quartile of the exposure distribution, and these effects have increased monotonically. Stronger associations were evident among premenopausal women for PCB-105 (OR=3.91, 95% CI 1.73-8.86) and for PCB-118 (OR=2.85, 95% CI 1.24-6.52) for the highest exposure category.

Also in the case-control study of the Long Island Hospital in New York [**Muscat 2003],** they measured the association between the total PCBs concentrations detected in adipose tissue and the risk of breast cancer in the participating women with a diagnosis of cancer. The highest tertile of the total PCB concentration was associated with an increased risk of relapse (RR=2.9, 95% CI 1.02-8.2) compared to the lower tertile.

Reviews and meta-analyses

In the reviews **[Brody 2007; Mouly 2016; Rodgers 2018]** the evidence for an association between PBCs and breast cancer risk in the general population is not conclusive.

But in a recent meta-analysis on exposure to different PCB congeners and breast cancer risk **[Zhang 2015]** the results of several epidemiological studies based on the classification of different congeners PCBs **[Wolff 1995]** in three different groups were evaluated; the PCBs belonging to group I with estrogenic effects, the PCBs belonging to group II with anti-estrogenic effects, the PCBs belonging to group III inducers of specific genes such as CYP1A and CYP2B on women with breast cancer. The results showed that the risk of breast cancer was statistically associated with the total exposure of the PCBs **[Zhang 2013]** to the PCBs congeners belonging to group II (with anti-estrogenic effects and immunotoxic congeners, similar to dioxin) and to groups of PCBs congeners belonging to group III (inducers Phenobarbital, CYP1A and CYP2B, biologically persistent), but not to PCBs congeners belonging to group I (potentially estrogenic).

However, in another meta-analysis **[Leng 2016]** the association between nine PCBs congeners and breast cancer was separately analyzed; the results of the meta-analysis imply that the PCB-99, PCB-183 and PCB-187 would increase the risk of breast cancer and have also found a significantly elevated risk in breast cancer among individuals with higher plasma/fat concentrations levels of PCB- 99, PCB-183 and PCB-187.

Co-funded by the Health Programme of the European Union

EU funding disclaimer: This project has received funding from the 3rd European Union Health Programme 201-2020 under Grant Agreement PP-2-5-2016 (# 769767)

References PCBs

- Gammon MD, Wolff MS, Neugut AI, et al. (2002) Environmental toxins and breast cancer on Long Island. II. Organochlorine compound levels in blood. Cancer Epidemiol Biomark Prev 11(8):686–697.
- Hoyer AP, Jørgensen T, Brock JW, Grandjean P (1998) Organochlorine exposure and risk of breast cancer. Lancet 352(9143):1816–1820.
- Hoyer AP, Jorgensen T, Grandjean P, Hartvig HB (2000). Repeated measurements of organochlorine exposure and breast cancer risk (Denmark). Cancer Causes Control, 11(2):177–84.
- Hoyer AP, Jørgensen T, Rank F, Grandjean P (2001) Organochlorine exposures influence on breast cancer risk and survival according to estrogen receptor status: a Danish cohort nested case-control study. BMC Cancer 1:8.
- Falck F Jr, Ricci A Jr, Wolff MS, Godbold J, Deckers P (1992). Pesticides and polychlorinated biphenyl residues in human breast lipids and their relation to breast cancer. Arch Environ Health, 47(2):143–6.
- Krieger N, Wolff MS, Hiatt RA, Rivera M, Vogelman J, Orentreich N (1994). Breast cancer and serum organochlorines: a prospective study among white, black, and Asian women. J Natl Cancer Inst, 86(8):589–99.
- Demers A, Ayotte P, Brisson J, Dodin S, Robert J, Dewailly E (2000). Risk and aggressiveness of breast cancer in relation to plasma organochlorine concentrations. Cancer Epidemiol Biomarkers Prev,9(2):161–6
- Demers A, Ayotte P, Brisson J, Dodin S, Robert J, Dewailly E (2002). Plasma concentrations of polychlorinated biphenyls and the risk of breast cancer: a congener- specific analysis. Am J Epidemiol,155(7):629–35.
- Wolff MS, Zeleniuch-Jacquotte A, Dubin N, Toniolo P (2000). Risk of Breast Cancer and Organochlorine Exposure. Cancer Epidemiology Biomarkers Prev, 9(3):271–7.
- Dorgan JF, Brock JW, Rothman N, Needham LL, Miller R, Stephenson HE Jr et al. (1999). Serum organochlorine pesticides and PCBs and breast cancer risk: results from a prospective analysis (USA). Cancer Causes Control, 10(1):1–11.
- Helzlsouer KJ, Alberg AJ, Huang HY, Hoffman SC, Strickland PT, Brock JW et al. (1999). Serum concentrations of organochlorine compounds and the subsequent development of breast cancer. Cancer. Epidemiol Biomarkers Prev, 8(6):525–32.
- Zheng T, Holford TR, Tessari J, Mayne ST, Owens PH, Ward B et al. (2000a). Breast cancer risk associated with congeners of polychlorinated biphenyls. Am J Epidemiol, 152(1):50–8.
- Zheng T, Holford TR, Mayne ST, Tessari J, Ward B, Carter D et al. (2000b). Risk of female breast cancer associated with serum polychlorinated biphenyls and 1,1-dichloro- 2,2′-bis(p-chlorophenyl)ethylene. Cancer Epidemiol Biomarkers Prev, 9(2):167–74.
- Holford TR, Zheng T, Mayne ST, Zahm SH, Tessari JD, Boyle P (2000). Joint effects of nine polychlorinated biphenyl (PCB) congeners on breast cancer risk. Int J Epidemiol, 29(6):975–82.
- Zhang Y, Wise JP, Holford TR, Xie H, Boyle P, Zahm SH et al. (2004). Serum polychlorinated biphenyls, cytochrome P-450 1A1 polymorphisms, and risk of breast cancer in Connecticut women. Am J Epidemiol, 160(12):1177–83.
- Rusiecki JA, Baccarelli A, Bollati V, Tarantini L, Moore LE, Bonefeld-Jorgensen EC (2008). Global DNA hypomethylation is associated with high serum-persistent organic pollutants in Greenlandic Inuit. Environ Health Perspect, 116(11):1547–52.
- Rubin CH, Lanier A, Kieszak S, Brock JW, Koller KR, Strosnider H et al. (2006). Breast cancer among Alaska Native women potentially exposed to environmental organochlorine chemicals. Int J Circumpolar Health, 65(1):18–27.
- Gatto NM, Longnecker MP, Press MF, Sullivan-Halley J, McKean-Cowdin R, Bernstein L (2007). Serum organochlorines and breast cancer: a case-control study among African-American women. Cancer Causes Control, 18(1):29–39.
- Itoh H, Iwasaki M, Hanaoka T, Kasuga Y, Yokoyama S, Onuma H et al. (2009). Serum organochlorines and breast cancer risk in Japanese women: a case-control study. Cancer Causes Control, 20(5):567–80.
- Ward EM, Schulte P, Grajewski B, Andersen A, Patterson DG Jr, Turner W et al. (2000). Serum organochlorine levels and breast cancer: a nested case-control study of Norwegian women. Cancer Epidemiol Biomarkers Prev, 9(12):1357–67.
- Laden F, Hankinson SE, Wolff MS, Colditz GA, Willett WC, Speizer FE et al. (2001a). Plasma organochlorine levels and the risk of breast cancer: an extended follow-up in the Nurses' Health Study. Int J Cancer, 91(4):568–74.

Co-funded by the Health Programme of the European Union

EU funding disclaimer: This project has received funding from the 3rd European Union Health Programme 201-2020 under Grant Agreement PP-2-5-2016 (# 769767)

- Raaschou-Nielsen O, Pavuk M, Leblanc A, Dumas P, Philippe Weber J, Olsen A et al. (2005). Adipose organochlorine concentrations and risk of breast cancer among postmenopausal Danish women. Cancer Epidemiol Biomarkers Prev, 14(1):67–74.
- Liljegren G, Hardell L, Lindström G, Dahl P, Magnuson A (1998). Case-control study on breast cancer and adipose tissue concentrations of congener specific polychlorinated biphenyls, DDE and hexachlorobenzene. Eur J Cancer Prev, 7(2):135–40.
- Moysich KB, Ambrosone CB, Vena JE, Shields PG, Mendola P, Kostyniak P et al. (1998). Environmental organochlorine exposure and postmenopausal breast cancer risk. Cancer Epidemiol Biomarkers Prev, 7(3):181–8.
- Millikan R, DeVoto E, Duell EJ, Tse CK, Savitz DA, Beach J et al. (2000). Dichloro diphenyl dichloro ethene, polychlorinated biphenyls, and breast cancer among African-American and white women in North Carolina. Cancer Epidemiol Biomarkers Prev, 9(11):1233–40.
- Lucena RA, Allam MF, Costabeber IH , Villarejo MLJ , Navajas RFC. Breast cancer risk factors: PCB congeners.European Journal of Cancer Prevention 2001, 10, 117-119
- Lopez-Carrillo L, Blair A, López-Cervantes M, Cebrián M, Rueda C, Reyes R et al. (1997) Dichloro diphenyl trichloro ethane Serum Levels and Breast Cancer Risk: A Case Control Study from Mexico' Cancer Res, 57(17):3728–32.
- Holmes AK, Koller KR et al. (2014) Case–control study of breast cancer and exposure to synthetic environmental chemicals among Alaska Native women. International Journal of Circumpolar Health 73, 257-60.
- Recio-Vega R, Velazco-Rodriguez V, Ocampo-Gómez G, Hernandez-Gonzalez S, Ruiz-Flores P, Lopez-Marquez F (2011). Serum levels of polychlorinated biphenyls in Mexican women and breast cancer risk. J Appl Toxicol, 31(3):270–8.
- Wolff MS, Toniolo PG (1995). Environmental organochlorine exposure as a potential etiologic factor in breast cancer. Environ Health Perspect, 103:Suppl 7: 141–5.
- Cohn BA, Terry MB, Plumb M, Cirillo PM (2012). Exposure to polychlorinated biphenyl (PCB) congeners measured shortly after giving birth and subsequent risk of maternal breast cancer before age 50. Breast Cancer Res Treat, 136(1):267–75.
- Zhang H, Liu L, Zhang P, Zhao Y, Wu X, Ni W. (2013). A case-control study on the relationship between Organochlorine and female breast cancer. Wei sheng yan jiu = Journal of hygiene research. 42(1):44–8.
- Charlier C, Pitance F, Plomteux G (2003). PCB residues in a breast cancer patient population. Bull Environ Contam Toxicol, 71(5):887–91.
- Charlier CJ, Albert AI, Zhang L, Dubois NG, Plomteux GJ (2004). Polychlorinated biphenyls contamination in women with breast cancer. Clin Chim Acta, 347(1-2):177–81.
- Stellman SD, Djordjevic MV, Britton JA, Muscat JE, Citron ML, Kemeny M et al. (2000). Breast cancer risk in relation to adipose concentrations of organochlorine pesticides and polychlorinated biphenyls in Long Island, New York. Cancer Epidemiol Biomarkers Prev, 9(11):1241–9.
- Aronson KJ, Miller AB, Woolcott CG, Sterns EE, McCready DR, Lickley LA et al. (2000). Breast adipose tissue concentrations of polychlorinated biphenyls and other organochlorines and breast cancer risk. Cancer Epidemiol Biomarkers Prev, 9(1):55–63.
- Muscat JE, Britton JA, Djordjevic MV, Citron ML, Kemeny M, Busch-Devereaux E et al. (2003). Adipose concentrations of organochlorine compounds and breast cancer recurrence in Long Island, New York. Cancer Epidemiol Biomarkers Prev, 12(12):1474–8.
- Wielsoe M, Kern P, Bonefeld-Jørgensen EC. (2017). Serum levels of environmental pollutants is a risk factor for breast cancer in Inuit: a case control study. Environmental Health1656.
- Arrebola JP, Belhassen H, Artacho-Cordón F, Ghali R, Ghorbel H, Boussen H, et al.(2015) Risk of female breast cancer and serumconcentrations of organochlorine pesticides and polychlorinated biphenyls: A case–control study in Tunisia Sci Total Environ 520:106–113.
- Leng L, et al. Polychlorinated biphenyls and breast cancer: a congener-specific meta-analysis. Environ Int. 2016;88:133–41.
- Zhang J, Huang Y, Wang X, Lin K, Wu K. (2015) Environmental Polychlorinated Biphenyl Exposure and Breast Cancer Risk: A Meta-Analysis of Observational Studies. PLoS One. 2015 Nov 10.
- Mouly TA, Toms LL. Breast cancer and persistent organic pollutants (excluding DDT): a systematic literature review. Environ Sci Pollut Res Int. 2016 Nov;23(22):22385-22407.
- IARC (2016). Polychlorinated biphenyls and polybrominated biphenyls. IARC Monogr Eval Carcinog Risk Chem Hum, Volume 107:1–503.
- Brody JG, Rudel RA, MS1 Michels KB, et al. (2007) Environmental Pollutants, Diet, Physical Activity, Body Size and Breast Cancer. CANCER Supplement June 15, 2007, Vol. 109, Number 12.
- Rodgers KM, Udesky JO, Rudel RA, Brody JG. Environmental chemicals and breast cancer: An updated review of epidemiological literature informed by biological mechanisms. Environmental Research 160, 152–182. 2018.

Co-funded by the Health Programme of the European Union

EU funding disclaimer: This project has received funding from the 3rd European Union Health Programme 201-2020 under Grant Agreement PP-2-5-2016 (# 769767)

3.2. Dichlorodiphenyltrichloroethane (DDT) and its metabolites (DDD, DDE) and others organochlorine compounds (Lindane, Hexachlorobenzene (HCB), Chlordane, ecc.)

Contaminants considered

Dichlorodiphenyltrichloroethane (DDT) is a synthetic industrial and household insecticide whose widespread use as a mosquito repellent and its long half-life made it a prominent environmental contaminant. Although DDT consequently helped lower incidence of malaria and typhoid, its use was banned in the US in 1972 for its effects on the environment and potential effects on human health. DDT and its main metabolites dichloro diphenyl dichloroethylene (DDE) and dichloro diphenyl dichloroethane (DDD) have endocrine disrupting properties.

Source

DDT is one of the most widely used insecticide in the world, successful in eradication of malaria from USA and other countries, though at an expense of devastating environmental problems and human health hazards. Between its first successful commercial applications in World War II and the severe usage restrictions in 1972, DDT was commonly used in households and agriculture because it does not wash off readily with water. It was the active ingredient in many aerosol fly sprays and a key ingredient in vegetable dusts and lawn and garden sprays.

Mean of exposure

Due to its extremely low solubility in water, DDT will be retained to a greater degree by soils and soil fractions with higher proportions of soil organic matter. It may accumulate in the top soil layer. Generally DDT is tightly sorbed by soil organic matter, but it (along with its metabolites) has been detected in many locations in soil and groundwater where it may be available to organisms.

Regulation and/or persistence

The EPA has assigned DDT, DDE, and DDD to Group B2, probable human carcinogens. The International Agency for Research on Cancer (IARC) has determined that DDT, DDE, and DDD are possibly carcinogenic to humans (Group 2B). The Department of Health and Human Services (DHHS) has determined that DDT, DDE, and DDD may reasonably be anticipated to be human carcinogens. In 1972, DDT was banned in the US, in 1978 in Italy. DDT is a very highly persistent organic pollutant in the environment that is readily adsorbed to soils and sediments.

Co-funded by the Health Programme of the European Union

EU funding disclaimer: This project has received funding from the 3rd European Union Health Programme 201-2020 under Grant Agreement PP-2-5-2016 (# 769767)

Evidence on (breast) cancer risk

DDT and DDE have been suggested to be associated with an increased risk of female breast cancer because of their reported estrogenic activity and ability to induce p450 enzymes, which are intimately involved in steroid hormone metabolism. Different case-control studies adjusted for some or all of the standard reproductive and demographic risk factors for breast cancer, such as BMI, adult body-weight gain, family history, menopausal status, age at menarche, age at first birth, and lactation history have shown a correlation between blood DDT/DDE levels and development of breast malignancy.

IARC Monography

The International Agency for Research on Cancer (IARC) published a Monograph on the evaluation of carcinogenic risk to humans “DDT, Lindane and 2,4-D” Vol. 113 (2018). The IARC evaluation of the carcinogenicity and exposure of DDT, Lindane and 2,4-D and breast cancer was considered in many scientific articles.

The relationship between serum concentration of DDT and his main metabolite DDE, and breast cancer has been evaluated in different case‑control studies.

For example, in the hospital-based case-control study conducted in 1994-1996 in Mexico **[Lopez-Carrillo 1997],** 141 cases aged between 20 and 79 years from participating hospitals and an equal number of controls without cancer were enrolled. Mean serum concentrations of 505.5 ng/g of lipids and 84.5 ng/g of lipids were reported for DDT (higher in controls) and DDE (higher in cases); the level of DDE found was not associated with the risk of breast cancer (OR=0.76, 95% CI 0.41-1.42); no risk data for DDT were reported.

The continuation of this study was carried out by **[Romieu 2000]** in Mexico by measuring serum DDE concentrations and DDT for a sub-sample of 120 breast cancer cases and 126 controls.

The concentration of DDE was higher in cases than in controls (but not statistically significant), whereas the concentration of DDT was not significantly higher in controls.

Another hospital-based case-control study was done in Rio de Janeiro, Brazil **[Mendonca 1999]**. In this study, women admitted with a diagnosis of breast cancer were enrolled as cases, and how hospital visitors are monitored without cancer. Cases and controls were interviewed in hospital and blood samples were obtained (before surgery for most cases) and analyzed for DDE and related compounds. Also in this case, no association between the risk of breast cancer and the increase in serum DDE was observed.

Also in another hospital study in New York, in the United States **[Wolff 2000a]** with cases of breast cancer and a control group of women undergoing surgery or biopsies for benign breast disease and a second control group of women without disease, concentrations of DDE and DDT determined in blood samples are not associated with the risk of breast cancer. In the same cohort, with an extended follow-up to 1994, only incident cases were considered.

Co-funded by the Health Programme of the European Union

EU funding disclaimer: This project has received funding from the 3rd European Union Health Programme 201-2020 under Grant Agreement PP-2-5-2016 (# 769767)

Cases with at least three annual blood samples were included and serum DDE concentrations were adjusted for lipids; 110 cases and 123 controls were included in the analysis **[Wolff 2000b]**. also in this case the results did not confirm a significant increased risk of breast cancer in relation to DDE.

[Moysich 1998] studied the association between breast cancer in postmenopausal women with serum concentrations of different organochlorine compounds DDE, HCB, PCBs in a case-control study in the state of New York, USA. Data on serum DDE and risk factors for breast cancer were available for 154 cases and 192 controls, the risk of breast cancer was increased in the highest category of DDE exposure (OR=1.34, 95% CI 0.71-2.55), but there was no significant trend of response to exposure (p for trend = 0.25).

A well designed case control study is that of **[Krieger 1994]** performed in Northern California, United States, with a long follow-up period (1964-1990). Among the 2097 patients identified with breast cancer, 150 cases (50 whites, 50 blacks and 50 Asians) were randomly selected and matched with 150 controls per race, age, date of entry and date of follow-up. After adjustment for reproductive factors, menopausal status and body mass index (BMI), there was no significant association between breast cancer risk and DDE serum concentrations for all subjects, including ethnic, white subgroups, blacks and Asians.

Also others case control studies conducted in USA **[Hunter 1997; Dorgan 1999; Helzlsouer 1999; Millikan 2000; Zheng 2000; Laden 2001; Gammon 2002; Gatto 2007]**, in Québec, Canada **[Demers 2000]**, in Hanoi, Vietnam **[Schecter 1997]**, in Naples, Italy **[Dello Iacovo 1999]**, in Norway **[Ward 2000]**, in Denmark **[Hoyer 1998]**, in Belgium **[Charlier 2003]**, in Slovakia **[Pavuk 2003]**, in Egypt **[Soliman 2003]**, in Alaska **[Rubin 2006]**, in Japan **[Iwasaki 2008; Itoh 2009]** found no association between serum DDE and DDT levels and breast cancer risk.
In the Canary Islands, Spain, **[Boada 2012]** found that serum levels of lindane were not associated with breast cancer; this study was not matched by age, cases were significantly older than controls, and few women were exposed.

Different case-control studies were conducted on the relationship between the concentration of DDE or DDT in adipose tissue and the risk of breast cancer in the USA **[Zheng 1999]**, in Ontario, Canada **[Aronson 2000]**, in Spain **[Ibarluzea 2004]**, in Denmark **[Raaschou-Nielsen 2005]**, in Sweden **[Liljegren 1998]**: in all these studies there was no association between the concentration of DDE or DDT found in adipose tissue and risk of breast cancer.

Co-funded by the Health Programme of the European Union

EU funding disclaimer: This project has received funding from the 3rd European Union Health Programme 201-2020 under Grant Agreement PP-2-5-2016 (# 769767)

Also **[van't Veer 1997]** in the EURAMIC (European community multicenter study) conducted in Germany, Netherlands, Northern Ireland, Switzerland, and Spain on breast cancer and exposure to DDE, after adjustment for BMI, age at first birth, current alcohol drinking, found no association between the concentration of DDE in adipose tissue and risk of breast cancer.

There are also case-control and/or cohort studies within the IARC monograph that found a statistically significant association between DDT exposure and its metabolites such as DDE and breast cancer. For example, the cohort study of **[Wolff 1993]** on women's health in New York enrolled 14,290 women between 1985 and 1991. During this time, women who had been diagnosed with breast cancer 1-6 months after entering the study were defined as cases. The controls were randomly selected by all cohort members who were alive and cancer-free at the time of cancer diagnosis and the serum concentrations of DDE and DDT were determined in a total of 58 cases and 171 controls; the concentration of DDE were statistically higher in cases of breast cancer compared to control subjects (DDE in cases: 11.0 +/- 9.1 ng/ml; DDE in controls: 7.7 +/- 6, 8 ng/ml, p = 0.031).

In the Danish cohort study **[Hoyer 2000]** a statistically significant serum concentration of p,p'-DDT was associated with a significantly greater risk of triple breast cancer and the relation to a dose-response was evident (OR=3.6, 95% CI 1.1-12.2). Within the same cohort, a total of 161 cases with ER status information and 318 matched controls who were free of breast cancer were included in an analysis according to ER status **[Hoyer 2001]**. The observed increased breast cancer risk associated with exposure to dieldrin concentration (ng/ml) derived from women who developed an estrogen receptor negative (ERN): OR=7.6, 95% CI 1.3-46.1, I vs. IV quartile.

In the hospital-based case-control study **[Contreras 1998]** conducted in Bogota, Colombia, women with incident breast cancer and controls were recruited from 1995-1996. Blood samples for the cases were obtained before treatment; plasma DDE was higher in cases than controls. The risk of breast cancer is increased with the plasma concentration of DDE (OR=1.95, 95% CI 1.10-3.52) for the third compared to the first tertile.

[Charlier 2004] studied the association between breast cancer and serum DDT and concentration of DDE and hexachlorobenzene (HCB) among 231 cases recruited from a hospital surgery unit and 290 age-matched controls seeking cytological screening in Belgium in 2001-2002. DDT, DDE and HCB were measured in serum, and both concentration levels were low compared to other studies. The presence of both organochlorine compounds (DDE and HCB) in serum was statistically significant associated with an increased risk of developing breast cancer, with OR=2.21 (95% CI 1.41-3.48) for the DDE and OR=4.99 (95% CI 2.95-8.43) for HCB).

Co-funded by the Health Programme of the European Union

EU funding disclaimer: This project has received funding from the 3rd European Union Health Programme 201-2020 under Grant Agreement PP-2-5-2016 (# 769767)

Several studies on human cancer on perinatal exposure to DDT have reported positive results.

In a prospective case–control study on young women (aged <20 years) in California, USA **[Cohn 2007]**, girls exposed to higher DDT/DDE levels were more likely to develop breast cancer than those with lower exposures, and risk increased with younger age at exposure. In this study they have found a positive trend between the serum level of p,p'-DDT (before it was banned, from 1959 to 1967) and the future risk of breast cancer (these women were mostly aged <20 years when DDT reached its peak of concentration). The number of identified cases (129) from the California registry, combined with the same controls, had breast cancer before age 50. Significant positive associations were found with p,p'-DDT in blood samples before diagnosis (µg/l 8.09-13.90), OR=2.5 (95% CI 1.0-6.3).
In a subsequent study based on this cohort **[Cohn 2015]**, the incidence of breast cancer in 9300 daughters of women who provided blood samples in the original study was examined in relation to maternal prenatal exposure to DDT. Serum peritoneal serum concentration of o,p'-DDT was significantly associated with the risk of breast cancer in daughters in models adjusted for maternal lipids, overweight and breast cancer history.

Reviews and meta-analyses

In the reviews of **[Snedeker 2001; Calle 2002]** most of the nested case-control and case-control studies conducted since 1996 have not confirmed previous observations of a significant positive relationship between serum or adipose tissue levels of DDE or DDT and cancer risk at the otherwise. Most of these studies were conducted using Caucasian women from the United States, Canada or Europe. Because some studies have documented a tendency of black women in the United States to have higher serum or DDE levels than white women, further studies are needed to determine if black women have a higher risk of breast cancer associated with body loads of DDE. One of the reasons for the lack of association between DDE levels in blood or tissues and the risk of breast cancer may be the route of exposure to different forms of DDT and its various estrogenic metabolites.

The scientific reviews of **[Macon 2013; Gray 2017]** point out that there are also different epidemiological studies that have found positive associations between DDT or its metabolites such as DDE in serum and an increased risk in developing breast cancer, resume the prospective studies conducted by **[Cohn 2007 and 2015]** where girls exposed to higher levels of DDT / DDE were more likely to develop breast cancer than those with lower exposures and the risk increased with younger age following exposure.

Co-funded by the Health Programme of the European Union

EU funding disclaimer: This project has received funding from the 3rd European Union Health Programme 201-2020 under Grant Agreement PP-2-5-2016 (# 769767)

In the two meta-analyzes on DDT and its metabolites DDE in general there are no big news and the risk of breast cancer **[Lopez-Cervantes 2004; Park 2014]** as they analyze the main scientific studies have already discussed in the previous paragraphs which are part of the most recent IARC monograph (2018) on the assessment of the human carcinogenic risk "DDT, Lindane and 2,4-D".
In the most recent meta-analysis **[Park 2014]** the scientific literature on exposure to DDT and its metabolites such as DDE and breast cancer risk was examined. In this meta-analysis, 35 case-control studies were analyzed and the overall result of the summary probability ratio (OR) for the identified studies was 1.03 (95% CI 0.95-12.12).

Subgroup analysis did not indicate a significant association between DDE exposure and breast cancer risk by design type, years of study, biological sample and geographical region of the study, except for case-population control studies based on estimation of DDE in serum published in the 90s.

References DDT

- Lopez-Carrillo L, Blair A, López-Cervantes M, Cebrián M, Rueda C, Reyes R et al. (1997) Dichloro diphenyl trichloro ethane Serum Levels and Breast Cancer Risk: A Case Control Study from Mexico' Cancer Res, 57(17):3728–32.
- Contreras OP, Rodríguez-Villamil J, Posso-Valencia HJ, Cortez JE. (1998) Organochlorine exposure and breast cancer risk in Colombian women Cad Saude Publica, 14:Suppl 3:125–32.
- Moysich KB, Ambrosone CB, Vena JE, Shields PG, Mendola P, Kostyniak P, et al. (1998) Environmental organochlorine exposure and postmenopausal breast cancer risk.Cancer Epidemiol Biomarkers Prev. 7(3):181–8.
- Mendonca GA, Eluf-Neto J, Andrada-Serpa MJ, Carmo PA, Barreto HH, Inomata ON et al. (1999). Organochlorines and breast cancer: a case-control study in Brazil. Int J Cancer, 83(5):596‑600.
- Dello Iacovo R, Celentano E, Strollo AM, Iazzetta G, Capasso I, Randazzo G (1999). Organochlorines and breast cancer. A study on Neapolitan women. Adv Exp Med Biol, 472:57‑66.
- Wolff MS, Zeleniuch-Jacquotte A, Dubin N, Toniolo P (2000a). Risk of breast cancer and organochlorine exposure. Cancer Epidemiol Biomarkers Prev, 9(3):271‑7.
- Romieu I, Hernandez-Avila M, Lazcano-Ponce E, Weber JP, Dewailly E (2000). Breast cancer, lactation history, and serum organochlorines. Am J Epidemiol, 152(4):363‑70.
- Schecter A, Toniolo P, Dai LC, Thuy LT, Wolff MS (1997). Blood levels of DDT and breast cancer risk among women living in the north of Vietnam. Arch Environ Contam Toxicol, 33(4):453‑6.
- Pavuk M, Cerhan JR, Lynch CF, Kocan A, Petrik J, Chovancova J (2003). Case-control study of PCBs, other organochlorines and breast cancer in Eastern Slovakia. J Expo Anal Environ Epidemiol, 13(4):267‑75.
- Soliman AS, Wang X, Di Giovanni J, Eissa S, Morad M, Vulimiri S et al. (2003). Serum organochlorine levels and history of lactation in Egypt. Environ Res, 92(2):110‑7.
- Wolff MS, Toniolo PG, Lee EW, Rivera M, Dubin N (1993). Blood levels of organochlorine residues and risk of breast cancer. J Natl Cancer Inst, 85(8):648‑52.
- Krieger N, Wolff MS, Hiatt RA, Rivera M, Vogelman J, Orentreich N (1994). Breast cancer and serum organochlorines: a prospective study among white, black, and Asian women. J Natl Cancer Inst, 86(8):589‑99.
- Hunter DJ, Hankinson SE, a F, Colditz GA, Manson JE, Willett WC et al. (1997). Plasma organochlorine levels and the risk of breast cancer. N Engl J Med, 337(18):1253‑8.
- Laden F, Hankinson SE, Wolff MS, Colditz GA, Willett WC, Speizer FE et al. (2001). Plasma organochlorine levels and the risk of breast cancer: an extended follow-up in the Nurses' Health Study. Int J Cancer, 91(4):568‑74.

Co-funded by the Health Programme of the European Union

EU funding disclaimer: This project has received funding from the 3rd European Union Health Programme 201-2020 under Grant Agreement PP-2-5-2016 (# 769767)

- Hoyer AP, Grandjean P, Jorgensen T, Brock JW, Hartvig HB (1998). Organochlorine exposure and risk of breast cancer. Lancet, 352(9143):1816‑20.
- Hoyer AP, Jorgensen T, Grandjean P, Hartvig HB (2000). Repeated measurements of organochlorine exposure and breast cancer risk (Denmark). Cancer Causes Control, 11(2):177‑84.
- Hoyer AP, Jorgensen T, Rank F, Grandjean P (2001). Organochlorine exposures influence on breast cancer risk and survival according to estrogen receptor status: a Danish cohort-nested case-control study. BMC Cancer, 1(1):8.
- Dorgan JF, Brock JW, Rothman N, Needham LL, Miller R, Stephenson HE Jr et al. (1999). Serum Organochlorine pesticides and PCBs and breast cancer risk: results from a prospective analysis (USA). Cancer Causes Control, 10(1):1‑11.
- Helzlsouer KJ, Alberg AJ, Huang HY, Hoffman SC, Strickland PT, Brock JW et al. (1999). Serum concentrations of organochlorine compounds and the subsequent development of breast cancer. Cancer Epidemiol Biomarkers Prev, 8(6):525‑32.
- Ward EM, Schulte P, Grajewski B, Andersen A, Patterson DG Jr, Turner W et al. (2000). Serum organochlorine levels and breast cancer: a nested case-control study of Norwegian women. Cancer Epidemiol Biomarkers Prev, 9(12):1357‑67.
- Iwasaki M, Inoue M, Sasazuki S, Kurahashi N, Itoh H, Usuda M et al.; Japan Public Health Center-based Prospective Study Group (2008). Plasma organochlorine levels and subsequent risk of breast cancer among Japanese women: a nested case-control study. Sci Total Environ, 402(2‑3):176‑83.
- Raaschou-Nielsen O, Pavuk M, Leblanc A, Dumas P, Philippe Weber J, Olsen A et al. (2005). Adipose organochlorine concentrations and risk of breast cancer among postmenopausal Danish women. Cancer Epidemiol Biomarkers Prev, 14(1):67‑74.
- Cohn BA, Wolff MS, Cirillo PM, Sholtz RI (2007). DDT and breast cancer in young women: new data on the significance of age at exposure. Environ Health Perspect, 115(10):1406‑14.
- Cohn BA, La Merrill M, Krigbaum NY, Yeh G, Park JS, Zimmermann L et al. (2015). DDT exposure in utero and breast cancer. J Clin Endocrinol Metab, 100(8):2865‑72.
- Wolff MS, Berkowitz GS, Brower S, Senie R, Bleiweiss IJ, Tartter P et al. (2000b). Organochlorine exposures and breast cancer risk in New York City women. Environ Res, 84(2):151‑61.
- Boada LD, Zumbado M, Henriquez-Hernandez LA, Almeida-Gonzalez M, Alvarez-Leon EE, Serra-Majem L et al. (2012). Complex organochlorine pesticide mixtures as determinant factor for breast cancer risk: a population-based case-control study in the Canary Islands (Spain). Environ Health, 11(1):28
- Charlier C, Albert A, Herman P, Hamoir E, Gaspard U, Meurisse M et al. (2003). Breast cancer and serum organochlorine residues. Occup Environ Med, 60(5):348‑51.
- Charlier C, Foidart JM, Pitance F, Herman P, Gaspard U, Meurisse M et al. (2004). Environmental dichlorodiphenyltrichlorethane or hexachlorobenzene exposure and breast cancer: is there a risk? Clin Chem Lab Med, 42(2):222‑7.
- Zheng T, Holford TR, Mayne ST, Tessari J, Ward B, Carter D et al. (2000). Risk of female breast cancer associated with serum polychlorinated biphenyls and 1,1-dichloro-2,2′-bis(p-chlorophenyl)ethylene. Cancer Epidemiol Biomarkers Prev, 9(2):167‑74.
- Itoh H, Iwasaki M, Hanaoka T, Kasuga Y, Yokoyama S, Onuma H et al. (2009). Serum organochlorines and breast cancer risk in Japanese women: a case-control study. Cancer Causes Control, 20(5):567‑80.
- Gatto NM, Longnecker MP, Press MF, Sullivan-Halley J, McKean-Cowdin R, Bernstein L (2007). Serum organochlorines and breast cancer: a case-control study among African-American women. Cancer Causes Control, 18(1):29‑39.
- Millikan R, DeVoto E, Duell EJ, Tse CK, Savitz DA, Beach J et al. (2000). Dichloro diphenyl dichloro ethene,polychlorinated biphenyls, and breast cancer among African-American and white women in North Carolina. Cancer Epidemiol Biomarkers Prev, 9(11):1233‑40.
- Gammon MD, Wolff MS, Neugut AI, Eng SM, Teitelbaum SL, Britton JA et al. (2002). Environmental toxins and breast cancer on Long Island. II. Organochlorine compound levels in blood. Cancer Epidemiol Biomarkers Prev, 11(8):686‑97.
- Demers A, Ayotte P, Brisson J, Dodin S, Robert J, Dewailly E (2000). Risk and aggressiveness of breast cancer in relation to plasma organochlorine concentrations. Cancer Epidemiol Biomarkers Prev, 9(2):161‑6.
- van't Veer P, Lobbezoo IE, Martin-Moreno JM, Guallar E, Gomez-Aracena J, Kardinaal AF et al. (1997). DDT (dicophane) and postmenopausal breast cancer in Europe: case-control study. BMJ, 315(7100):81‑ 5.

Co-funded by the Health Programme of the European Union

EU funding disclaimer: This project has received funding from the 3rd European Union Health Programme 201-2020 under Grant Agreement PP-2-5-2016 (# 769767)

- Liljegren G, Hardell L, Lindstrom G, Dahl P, Magnuson A (1998). Case-control study on breast cancer and adipose tissue concentrations of congener specific polychlorinated biphenyls, DDE and hexachlorobenzene. Eur J Cancer Prev, 7(2):135‑40.
- Zheng T, Holford TR, Mayne ST, Owens PH, Ward B, Carter D et al. (1999). Beta-benzene hexachloride in breast adipose tissue and risk of breast carcinoma. Cancer, 85(10):2212–8.
- Aronson KJ, Miller AB, Woolcott CG, Sterns EE, McCready DR, Lickley LA et al. (2000). Breast adipose tissue concentrations of polychlorinated biphenyls and other organochlorines and breast cancer risk. Cancer Epidemiol Biomarkers Prev, 9(1):55–63.
- Ibarluzea JM, Fernandez MF, Santa-Marina L, Olea-Serrano MF, Rivas AM, Aurrekoetxea JJ et al. (2004). Breast cancer risk and the combined effect of environmental estrogens. Cancer Causes Control, 15(6):591‑600.
- Rubin CH, Lanier A, Kieszak S, Brock JW, Koller KR, Strosnider H et al. (2006). Breast cancer among Alaska Native women potentially exposed to environmental organochlorine chemicals. Int J Circumpolar Health, 65(1):18‑27.
- Lopez-Cervantes M, Sanchez LT, Tobías A, Carrillo LL. (2004) Dichlorodiphenyldichloroethane Burden and Breast Cancer Risk: A Meta-Analysis of the Epidemiologic Evidence. EHP, Vol. 112, N. 2.
- Park JH, Cha ES, Ko Y, Hwang MS , Hong JH, Lee WJ. (2014) Exposure to Dichlorodiphenyltrichloroethane and the Risk of Breast Cancer: A Systematic Review and Meta-analysis. Osong Public Health Res Perspect 5(2), 77 – 84.
- Macon MB, Fenton SE. (2013) Endocrine disruptors and the breast: early life effects and later life disease. J Mammary Gland Biol Neoplasia. ;18(1):43-61.
- Snedeker SM. (2001) Pesticides and Breast Cancer Risk: A Review of DDT, DDE, and Dieldrin EHP, Vol. 109, Supplement 1.
- Calle EE, Frumkin H, Henley SJ, Savitz DA, Thun MJ. (2002) Organochlorines and Breast Cancer Risk. CA Cancer J Clin. Sep-Oct;52(5):301-9.
- Gray JM , Rasanayagam S, Engel C and Rizzo J. (2017) State of the evidence 2017: an update on the connection between breast cancer and the environment. Environmental Health, 16:94.
- IARC (2018). DDT, LINDANE, AND 2,4-D. IARC Monogr Eval Carcinog Risk Chem Hum, Volume 113:1 503.

Co-funded by the Health Programme of the European Union

EU funding disclaimer: This project has received funding from the 3rd European Union Health Programme 201-2020 under Grant Agreement PP-2-5-2016 (# 769767)

3.3. Dioxin (TCDD)

Contaminants considered

TCDD is a chlorinated polycyclic hydrocarbon which is a product of combustion pollution and production chemicals, one of the most notorious organochlorines is 2,3,7,8-tetrachloridibenzo-p-dioxin (TCDD or dioxin). Agent Orange, the herbicide used by the United States Army in the Vietnam War, was found to be tainted by TCDD. TCDD is found in soil and water and, due to its lipophilic properties and the extended half-life of approximately 7-8 years in humans, TCDD bioaccumulates in animals and the environment. TCDD binds to the aromatic hydrocarbon receptor (AHR) and has anti-estrogenic properties. There are many other environmental contaminants that bind to AHR and their hazard levels are based on their effects related to TCDD or equivalent toxicity factor

Source

Dioxins are widespread environmental contaminants. They are produced by paper and pulp bleaching; incineration of municipal, toxic, and hospital wastes; certain electrical fires; and smelters (plants where metal is extracted from ores). They are also found as a contaminant in some insecticides, herbicides, and wood preservatives.

Mean of exposure

A particular dioxin that is likely to be carcinogenic to humans is called TCDD (2,3,7,8-tetrachlorodibenzo-pdioxin). The general population is exposed to low levels of TCDD primarily from eating dairy products, fish, and meat, including poultry. TCDD has a half-life of 7–9 years in humans. Due to the omnipresence of dioxins, all people have background exposure and a certain level of dioxins in the body, leading to the so-called body burden. Current normal background exposure is not expected to affect human health on average.

Regulation and/or persistence

TCDD was classified by IARC as a "known human carcinogen". However, TCDD does not affect genetic material and there is a level of exposure below which cancer risk would be negligible. However, due to the high toxic potential of this class of compounds, efforts need to be undertaken to reduce current background exposure. In 2001, the Joint Food and Agriculture Organization of the United Nations (FAO)/WHO Expert Committee on Food Additives (JECFA) performed an updated comprehensive risk assessment of PCDDs, PCDFs, and “dioxin-like” PCBs. In order to assess long- or short-term risks to health due to these substances, total or average intake should be assessed over months, and the tolerable intake should be assessed over a period of at least 1 month. The experts established a provisional tolerable monthly intake (PTMI) of 70 picogram/kg per month. This level is the amount of dioxins that can be ingested over lifetime without detectable health effects.

Co-funded by the Health Programme of the European Union

EU funding disclaimer: This project has received funding from the 3rd European Union Health Programme 201-2020 under Grant Agreement PP-2-5-2016 (# 769767)

Evidence on (breast) cancer risk

The few epidemiologic studies that examined the relationship between TCDD exposure and breast cancer risk are limited by small sample size and lack of individual exposure data. Breast cancer mortality and incidence increased in female workers employed in the production of TCDD-contaminated phenoxyherbicides.

Significantly increased mortality from breast cancer was reported in Chapaevsk (Samara Region, Russia) with a chemical plant known to be a source of TCDD because from 1967 to 1987 it produced hexachlorocyclohexane (lindane) and its derivatives **[Revich 2001]** so dioxins were detected in air, in soil, in the town's drinking water, in the cow's milk and in human blood samples. To assess cancer risk and reproductive health status, official medical statistical information was used. Chapaevsk women have a SMR higher risk overall due to breast cancer (SMR=2.1, 95% CI 1.6-2.7) and cervix cancer (SMR=1.8, 95% CI 1.0-3.1). Chapaevsk is an incredibly interesting site for further environmental-epidemiological research to assess the impact of dioxins on human health.

Two ecological studies **[Benko 2009]** analyzed the incidence of selected malignancies in two populations exposed to polychlorinated hydrocarbons, mostly TCDDs/Fs and PCBs, by comparing data available in the National Cancer Registry of the Slovak Republic and National Oncological Registry of the Czech Republic databases.
Neither TCDDs/Fs appear to contribute to the observed incidence of breast and prostate cancer in the Michalovce District and lower bladder cancer incidence in Uherske Hradiste District.

The purpose of a case-control study **[Viel 2008]** in the southwest border of Besançon (France) was to examine the association between dioxins emitted from a polluting urban solid waste incinerator (MSWI) and the risk of invasive breast carcinoma between women living in the area under the direct influence of the structure. They compared 434 incident cases of invasive breast cancer diagnosed between 1996 and 2002, and 2170 controls randomly selected from the 1999 population census. In this study, a dispersion model validated as a proxy for dioxin exposure was used, resulting in four exposure categories. Furthermore, by means of GIS (Geographic Information System) technology they used dioxin concentrations as relative data rather than absolute figures to estimate past exposure. These geographic exposure categories were evaluated by PCDD/F measurements from soil samples. No increased or decreased risk for breast cancer was found for any dioxin exposure category.

Co-funded by the Health Programme of the European Union

EU funding disclaimer: This project has received funding from the 3rd European Union Health Programme 201-2020 under Grant Agreement PP-2-5-2016 (# 769767)

In the interesting ecological study on the population **[Verkasalo 2004]** carried out in the neighboring areas (<20.0 km) of the river Kymijoki (heavily contaminated) in the south of Finland, at the beginning of the eighties, the association between dibenzo-p- polychlorinated dioxins and dibenzofurans and different types of cancer, including breast cancer, particularly in the category of farmers living near the river, was investigated. They used the GIS method to map the registry data, in squares of 500 m × 500 m from 1981 to 2000. For breast cancer they found a RR=1.15 (95% CI 1.03-1.28) for those who live at a distance from the river less than 5 km (1.0-4.9 km).

In the ecological study done in Michigan, USA **[Dai 2008]** it was found that there is a strong association between high levels of incidence and aging of breast cancer near areas contaminated by high levels of dioxin in the soil. These results suggest that the increase in breast cancer incidence is spatially associated with dioxin contamination in the soil. Aging is a substantial factor in the development of breast cancer. Tests can be used for high surveillance and education, as well as formulating new study hypotheses for further research.

Another interesting ecological study on the population in the same area of Michigan, USA **[Guajardo 2009]** evaluated the previously determined geographical groups of incidence of breast and lung cancer among residents living near the Tittabawassee and Saginaw rivers using a new series of environmental factors. Breast cancer data was acquired by the Michigan Department of Health, along with data from point sources from the United States Environmental Protection Agency (EPA). The data sets were used to determine whether there is a spatial association between the risk of disease and the environmental contamination of several persistent contaminants, including dioxins. Data georeferencing techniques were used and statistical analyzes were performed to investigate the local risk of breast and lung cancer.
The study shows that the neighborhoods (indicated with their zip code) in the immediate vicinity of the rivers were associated with a high risk of breast cancer, while an increased risk of lung cancer was detected among the neighborhoods in the immediate vicinity of pollution point sources and main motorways. In addition, the report on cancer statistics from the Institute of Public Health in Michigan shows that the counties of Midland and Saginaw (which contain the ZIP codes 48640, 48603, 48734, 48880, 48618 and 48732) had a higher rate of adjusted breast for the incidence of cancer in the period from 1994 to 2003 compared to the incidence rates in Bay County (located further away from the Tittabawassee river). High rates of breast cancer incidence were observed in ZIP code 48640 (OR=1.76, 95% CI 1.31–2.33), ZIP code 48603 (OR=1.65, 95% CI 1.23–2.20) and ZIP code 48734 (OR=1.88, 95% CI 1.34-2.63), all located near rivers and industrial facilities potentially responsible for environmental contamination of rivers. Finally, statistically significant cancer incidence clusters ($p \leq .001$) were observed among residents living near the rivers.
These findings are useful for researchers and government agencies for risk assessment, regulation and control of environmental contamination in floodplains.

Co-funded by the Health Programme of the European Union

EU funding disclaimer: This project has received funding from the 3rd European Union Health Programme 201-2020 under Grant Agreement PP-2-5-2016 (# 769767)

IARC Monography

The International Agency for Research on Cancer (IARC), in the Monograph on the evaluation of carcinogenic risk to humans "Polychlorinated dibenzo-para-dioxins and Polychlorinated Dibenzofurans" Vol. 69 (1997) and in the Vol. 110F (2012), carried out an evaluation to investigate the association between TCDD exposure and cancer in humans.

The IARC evaluation of the carcinogenicity of TCDD it is unique because more emphasis is given to all cancers combined, compared to specific site cancer, then results for all cancers do not refer to individual specific cancer sites. 2,3,7,8-Tetrachlorodibenzo-para-dioxin (TCDD) is the most potent dioxin. In IARC's evaluations, evidence of a causal association with TCDD exposure was considered strongest for lung cancer, non-Hodgkin's lymphoma (NHL), and soft-tissue sarcoma (STS) and all cancers combined in occupationally exposed populations **[IARC 2012]**. As a comparison, typical blood levels of TCDD in adults without known sources of exposure fall in the range of 1–10 ppt **[IARC 1997]**.

Reviews

Exposure to TCDD and breast cancer risk has been examined in detail by several review authors **[Laden 1998; Birnbaum 2003; Boffetta 2011; Jenkins 2012; Macon 2013]** without substantial evidence of increased risk. The review of **[Laden 1998]** on ecological studies highlights in particular the two studies following the accidental explosion at a chemical plant near Seveso, Italy, in 1976, where exposure to high levels of dioxin in the environment is assessed **[Bertazzi 1993 and 1997]** studying both mortality and incidence of cancer during the decade following the event and, in particular, no excess in incidence or mortality for breast cancer was observed in studies based on the population of Seveso residents. Though in a subsequent follow-up study **[Pesatori 2009]** of the incidence of cancer covering the period 1977-1996 including the subjects residing at the time of the accident in three contaminated areas with decreasing ground TCDD levels was updated (zone A, very high; zone B, high; zone R, low) also in an uncontaminated surrounding area of reference,the incidence of cancer did not differ from expectations in any of the contaminated areas, but for breast cancer an increased risk was found in zone A for females 15 years after the accident (five cases, RR=2.57, 95% CI 1.07-6.20).

The extension of the Seveso cancer incidence study confirmed an excess risk of neoplasia of the lymphatic and hematopoietic tissue in the most exposed areas. The high risk of breast cancer in females in Zone A after 15 years from the Seveso accident deserves a further in-depth investigation. In the review of **[Boffetta 2011]** two studies comparing TCDD level in breast adipose tissue among women with cancer and benign disease reported no statistically significant difference **[Hardell 1996; Reynolds 2005].** Overall, the evidence linking TCDD exposure to breast cancer risk is inconclusive in this review.

Co-funded by the Health Programme of the European Union

EU funding disclaimer: This project has received funding from the 3rd European Union Health Programme 201-2020 under Grant Agreement PP-2-5-2016 (# 769767)

In the review of **[Macon 2013]** other population studies investigating the effects of high TCDD exposure in the Seveso area in Italy were examined: for example, the **[Warner 2002]** study found that women in the area have an increased risk of breast cancer even if not statistically significant, furthermore a subsequent follow-up assessment of that population **[Boffetta 2011]** found no association between TCDD exposure and breast cancer incidence or mortality. Many of the girls who had been exposed to high levels of TCDD had not reached postmenopausal age (age at maximum risk of breast cancer in the normal population) at the time of data analysis, and it is possible that the reported results were underestimated. Therefore, a follow-up study to determine whether these women developed breast cancer would be useful to accurately assess the TCDD exposure-related health outcome .

References Dioxin (TCDD)

- Warner M, Eskenazi B, Mocarelli P, et al. (2002) Serum dioxin concentrations and breast cancer risk in the Seveso Women's Health Study. Environ Heal Perspect.;110(7):625–8.
- Boffetta P, Mundt KA, Adami HO, Cole P, Mandel JS. TCDD and cancer: a critical review of epidemiologic studies. Crit Rev Toxicol. 2011;41(7):622–36.
- IARC (1997). Polychlorinated dibenzo-para-dioxins IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, Vol. 69. Polychlorinated Dibenzo-para-dioxins and Polychlorinated Dibenzofurans. Lyon: IARC, 33–343.
- Laden F, Hunter DJ. (1998). Environmental risk factors and female breast cancer. Annu Rev Public Health 19:101–123.
- Bertazzi A, et al. (1993). Cancer incidence in a population accidentally exposed to 2,3,7,8-tetrachlorodibenzo-para-dioxin. Epidemiology 4:398–406.
- Bertazzi A, Zocchetti C, Guercilena S, Consonni D, Tironi A, et al (1997). Dioxin exposure and cancer risk: a 15-year mortality study after the "Seveso accident" Epidemiology.;8(6):646-52.
- Macon MB & Fenton SE. (2013) Endocrine Disruptors and the Breast: Early Life Effects and Later Life Disease. J Mammary Gland Biol Neoplasia 18:43–61.
- Hardell L, et al. (1996). Increased concentrations of octachlorodibenzo-p-dioxin in cases with breast cancer—Results from a case-control study. Eur J Cancer Prev 5:351–357.
- Reynolds P, et al. (2005). Regional variations in breast cancer incidence among California women, 1988–1997. Cancer Causes Control 16:139–150.
- Pesatori AC, Consonni D, Rubagotti M, Grillo P, Bertazzi PA. (2009) Cancer incidence in the population exposed to dioxin after the "Seveso accident": twenty years of follow-up. Environ Health. 15;8:39.
- Dai D, Oyana TJ. (2008) Spatial variations in the incidence of breast cancer and potential risks associated with soil dioxin contamination in Midland, Saginaw, and Bay Counties, Michigan, USA. Environmental Health, 7:49
- Revich B, Aksel E, Ushakova T, Ivanova I, Zhuchenko N, Klyuev N, Brodsky B, Sotskov Y. (2001) Dioxin exposure and public health in Chapaevsk, Russia. Chemosphere ;43(4-7):951-66.
- Bencko V, Rames J. et al. (2009) Human exposure to polyhalogenated hydrocarbons and incidence of selected malignancies – central European experience. Neoplasma 56, 4.
- Viel JF, Clément MC, Hägi M, Grandjean S, Challier B, Danzon A. (2008) Dioxin emissions from a municipal solid waste incinerator and risk of invasive breast cancer: a population-based case-control study with GIS-derived exposure Int J Health Geogr. 28;7:4.
- Verkasalo PK, Kokki E, Pukkala E, Vartiainen T, Kiviranta H, Penttinen A, Pekkanen J. (2004) Cancer Risk Near a Polluted River in Finland. Environ Health Perspect. 112(9):1026–1031.
- Guajardo OA and Oyana TJ. (2009) A Critical Assessment of Geographic Clusters of Breast and Lung Cancer Incidences among Residents Living near the Tittabawassee and Saginaw Rivers, Michigan, USA Journal of Environmental and Public Health 1-16 pages.
- Jenkins S, Betancourt AM, Wang J, Lamartiniere CA. (2012) Endocrine-active chemicals in mammary cancer causation and prevention. J Steroid Biochem Mol Biol.;129(3-5):191-200.
- Birnbaum LS, Fenton SE.(2003) Cancer and developmental exposure to endocrine disruptors. EHP 111
- IARC (2012). Monographs on the Evaluation of Carcinogenic Risks to Humans, volume 100F: 2,3,7,8-Tetrachloro dibenzo para - dioxin, 2,3,4,7,8-pentachlorodibenzofuran, and 3,3′,4,4′,5-pentachloro biphenyl. Lyon, France: International Agency for Research on Cancer.

Co-funded by the Health Programme of the European Union

EU funding disclaimer: This project has received funding from the 3rd European Union Health Programme 201-2020 under Grant Agreement PP-2-5-2016 (# 769767)

3.4.Polycyclic Aromatic Hydrocarbons (PAH)

Contaminants considered

Polycyclic aromatic hydrocarbons (PAHs) are a group of several hundred organic chemically related compounds ubiquitous environmental pollutants generated primarily during the incomplete combustion of organic materials (e.g. coal, oil, petrol, and wood). Chemically the PAHs are comprised of two or more benzene rings bonded in linear, cluster, or angular arrangements. Although there are many PAHs, most regulations, analyses, and data reporting focus on only a limited number of PAHs, typically between 14 and 20 individual PAH compounds.

Source

Polycyclic aromatic hydrocarbons (PAHs) enter the environment through various routes, they are ecologically persistent, have different toxic effects based on their molecular structure on organisms through various actions. The general characteristics of PAHs are high melting and boiling points (therefore they are solid), low vapor pressure and very low aqueous solubility, also very soluble in organic solvents (highly lipophilic). PAHs also exhibit various functions such as light sensitivity, heat resistance, conductivity; It emits skills, resistance to corrosion and physiological action.

The atmosphere is the most important means of ubiquitous dispersal of PAHs in the environment, as PAHs are emitted into the atmosphere mainly by the incomplete combustion of organic matter. The combustion of sources can be natural (including volcanoes and forest fires) or anthropogenic (such as vehicle discharges, agricultural fires, power plants, coke plants, steel mills, foundries and other industrial sources). PAHs tend to be in higher concentrations in urban environments than in rural areas because most PAH sources are located in or near urban centers. Clearly the PAHs present in the atmosphere suffer the effect of dry and wet deposition that makes them deposit in the soil and in the water. Some of these PAHs come from nearby sources, such as the exhaust gases of adjacent cars, while others come from more distant sources and have been transported at various distances through the air.

Mean of exposure

The main route of exposure of PAHs in the population goes through the exposure of contaminants in the atmosphere both in the outdoor and indoor environment, in the soil passing to water through for example industrial effluents and accidental spills during the transport of oil at sea. In addition, PAHs can be contained by eating smoked or grilled foods (principally meat), smoking cigarettes or breathing smoke from open fireplaces with wood and/or pellets. **[ACGIH 2005]**. Routes of exposure include ingestion, inhalation and skin contact in occupational and non-occupational settings. Occupational exposure can also occur in workers who breathe exhaust gases, such as mechanics, street vendors, motor vehicle drivers, including workers in mining, metalworking or oil refining. People may be exposed to PAHs in the air and in the surface soil by direct inhalation, ingestion or skin contact.

Co-funded by the Health Programme of the European Union

EU funding disclaimer: This project has received funding from the 3rd European Union Health Programme 201-2020 under Grant Agreement PP-2-5-2016 (# 769767)

Regulation and/or persistence

US government agencies have regulations that are relevant to workplace PAH and environmental exposures. In 2000, EPA **[U.S.EPA. 2000]** established environmental water quality criteria to protect human health from the carcinogenic effects of exposure to PAHs. The objective of these criteria was to set an undetectable level (zero concentration for carcinogenic PAHs in ambient water).

The EPA developed a maximum level of contaminants (MCL) for benzo (a) pyrene at 0.2 ppb. It is known that benzo (a) pyrene (BaP) is the most carcinogenic PAH.

The WHO orientation **[WHO 2003]** established the unit risk of lung carcinoma of BaP at 87x10-6 ng/m³ for lifetime exposure. According to many WHO member states, the reference values for BaP are between 0.1 and 1.3 ng/m³. According to the European Commission **[European Commission, Directive 2004/107/EC]**, the average annual target concentration should not be exceeded in the fraction of PM10 in 1 ng/m³ although unfortunately this objective has been exceeded in many European locations, in particular in the eastern countries.

Evidence on (breast) cancer risk

PAH have been shown to cause carcinogenic and mutagenic effects and are potent immunosuppressants. Effects have been documented on immune system development, humoral immunity and on host resistence. The most extensively studied PAHs are benzo(a)pyrene (BaP) and 7,12-dimethylbenzo anthracene (DMBA).

Like many other environmental chemicals that are associated with breast cancer risk, PAHs are lipophilic (fat-seeking) and are stored in the fat tissue of the breast. PAHs have been shown to increase risk for breast cancer through a variety of mechanisms.

DMBA (7,12-Dimethylbenz(a)anthracene) is commonly found in our environment and can be isolated from diesel exhaust, barbequed meat, tobacco smoke, overheated cooking oil, etc.

Several recent studies have reported that PAHs (estrogen-mimicking) can activate estrogen receptors (ER), either directly or indirectly, by producing estrogenic metabolites **[Pliskova 2005]**

Several population studies have examined the role of polycyclic aromatic hydrocarbons and the risk of breast cancer. The case-control study conducted at Long Island (LIBCSP) found a statistically significant increase for women with breast cancer with detectable levels of PAH-DNA adducts in the blood **[Gammon 2002, 2004]** and estimated an increase of breast cancer risk for women in the higher quintile than the lower one of PAH-DNA adducts.

In another study, elevated PAH-DNA adducts measured in breast cancer tissue were significantly associated with breast cancer (OR=2.56, 95% CI 1.05-6.24) **[Perera 2003]**.

Co-funded by the Health Programme of the European Union

EU funding disclaimer: This project has received funding from the 3rd European Union Health Programme 201-2020 under Grant Agreement PP-2-5-2016 (# 769767)

Also the recent nested case–control study conducted in New York **[Shen 2017]** examined the association between polycyclic aromatic hydrocarbon (PAH)-albumin adducts in blood (80 cases and 156 controls). In this study 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 and there was a dose–response relationship with women with higher levels of PAH exposure having more than a fourfold increase in risk.

However, two cohort studies have not observed any association between PAHs and the risk of breast cancer that could be due to the measurement of non-carcinogenic PAH markers in urine where urinary measurements only reflect term exposure **[Lee 2010]** or in samples of blood **[Saieva 2011]**.

An increasing number of studies have found that exposure to PAHs may further increase the risk of breast cancer for women with high susceptibility to genetic variants involved in carcinoma metabolism, DNA repair and cell cycle control pathways **[Terry 2004]**. These stronger associations in subgroups defined by genetic variants suggest that even women with a higher risk of breast cancer based on family history would be at greater risk, but detecting interactions between environmental carcinogens and underlying risk requires a sufficient number of women. It has been hypothesized that women at greater risk of breast cancer from exposure to PAH are women who have a higher underlying inherent risk of breast cancer, predicted by their family history of cancer **[Terry 2004]**.

The genetic differences in DNA repair genes can lead to differences in cancer susceptibility and may change the impact of environmental exposures on cancer risk.
Soil measurements will likely reflect PAH concentrations in the air because the deposition of PAHs is proportional to airborne concentrations above the ground. The concentrations of BaP in the soil may be more stable and do not vary as much as the airborne exposures **[Shantakumar 2005]**.
The season of blood donation and smoking status are the strongest predictors of detectable adducts to PAH DNA. Other predictive factors are increased age, higher income, early age at menarche, fewer months of breastfeeding and BaP of the soil. Halogenated and non-halogenated polycyclic aromatic hydrocarbons (HAH/PAH), such as polychlorinated dibenzo-p-dioxins and biphenyls and benzo (a) pyrene, have been recognized as significant and widespread environmental contaminants that induce AhR expression in target tissues, especially in the womb **[Pliskova 2005].**

Co-funded by the Health Programme of the European Union

EU funding disclaimer: This project has received funding from the 3rd European Union Health Programme 201-2020 under Grant Agreement PP-2-5-2016 (# 769767)

IARC Monography

The International Agency for Research on Cancer (IARC) in the Monograph on the evaluation of carcinogenic risk to humans “Some non-heterocyclic polycyclic aromatic hydrocarbons and some related exposures.” Vol. 92 (2010) and in the Monograph “Bitumens and Bitumen Emissions, and Some N– and S-Heterocyclic Polycyclic Aromatic Hydrocarbons.” Vol. 103 (2013) carried out an evaluation to investigate the association between PAH exposure and cancer in humans.

More than 60 individual PAHs were evaluated by IARC in Vol. 103 (2013) and others in Vol. 92 (2010). As noted in these Volumes, the mechanisms of action of the various PAHs vary: some are carcinogenic, some are not, and some are mutagenic, and some are not. There are at least three pathways by which these compounds are metabolized, and various PAHs are metabolized preferentially by various pathways. It is not clear how these compounds would be evaluated as a group because: (a) they have already been evaluated individually; and (b) the complex mixtures in which they occur are rarely analysed for the concentrations of more than a few PAHs. Polycyclic aromatic hydrocarbons are environmental contaminants that play an important carcinogenic role due to widespread population exposure; these persistent contaminants can be bio-transformed into reactive intermediates that form covalent PAH-DNA adducts that have mutagenic properties to initiate and/or promote tumorigenesis **[Phillips 1983; IARC 2010].**

Evidence suggests that exposure to PAHs has a causational effect on breast cancer in humans, yet this interaction is not clearly understood.

Review

The review of **[Korsh 2015]** examines the potential relationship between PAHs and breast cancer; it is also crucial to consider the geographic location and socioeconomic status of the patients. Studies conducted in Western New York in 2005 and 2007 have noted the necessity of investigating exposure to PAHs in relation to the location where patients resided during various critical periods in their lives, such as at the times of menarche and first birth **[Bonner 2005].**

Furthermore, in response to reports of high breast cancer mortality rates in the North eastern USA, a 1997 study of the region was conducted; this study found statistically significant clusters of breast cancer deaths in the New York City-Philadelphia metropolitan area, particularly in affluent suburban communities with ample access to health care **[Kulldorff 1997]**.

The researchers noted that they were unaware of any studies indicating greater exposure to PAHs in these communities, but it is nonetheless worth considering environmental conditions as a contributing factor to breast cancer mortality rates, as such factors can vary widely with location. Subsequent research conducted among breast cancer patients in one of such significant suburban cluster – Long Island, NY – reported that PAH-DNA adduct levels were higher, albeit not significantly, among this area’s breast cancer patients than in the control population **[Gammon 2002]**.

Co-funded by the Health Programme of the European Union

EU funding disclaimer: This project has received funding from the 3rd European Union Health Programme 201-2020 under Grant Agreement PP-2-5-2016 (# 769767)

References Polycyclic Aromatic Hydrocarbons (PAH)

- Bonner MR, Han D, Nie J, Rogerson P, Vena JE, Muti P, Trevisan M, Edge SB, Freudenheim JL: Breast cancer risk and exposure in early life to polycyclic aromatic hydrocarbons using total suspended particulates as a proxy measure. Cancer Epidemiol Biomarkers Prev 2005; 14: 53–60.
- Kulldorff M, Feuer EJ, Miller BA, Freedman LS: Breast cancer clusters in the northeast United States: a geographic analysis. Am J Epidemiol 1997; 146: 161–170.
- IARC (2010). Some non-heterocyclic polycyclic aromatic hydrocarbons and some related exposures, Monogr Eval Carcinog Risks Hum 92 (2010) 765–771.
- ACGIH (American Conference of Governmental Industrial Hygienists). Polycyclic aromatic hydrocarbons (PAHs) biologic exposure indices (BEI) Cincinnati. OH: American Conference of Governmental Industrial Hygienists; 2005.
- WHO (World Health Organization). Polynuclear aromatic hydrocarbons in drinking-water. Background document for development of WHO Guidelines for Drinking-water Quality; 2003 [WHO/SDE/WSH/03.04/59].
- European Commission, Directive 2004/107/EC of the European Parliament and of the Council of 15 December 2004 relating to arsenic, cadmium, mercury, nickel and polycyclic aromatic hydrocarbons in ambient air, Off J L023 (2005) 0003–0016 [26/01/2005].
- U.S.EPA. 2000.Deposition of Air Pollutants to the Great Waters: Third Report to Congress. Office of Air Quality Planning and Standards. EPA-453/R-00-0005; June 2000.
- Phillips DH (1983) Fifty years of benzo(a)pyrene. Nature 303(5917): 468–472.
- Gammon MD, Santella RM, Neugut AI, Eng SM, Teitelbaum SL, Paykin A, Levin B, Terry MB, Young TL, Wang LW, Wang Q, Britton JA, Wolff MS, Stellman SD, Hatch M, Kabat GC, Senie R, Garbowski G, Maffeo C, Montalvan P, Berkowitz G, Kemeny M, Citron M, Schnabel F, Schuss A, Hajdu S, Vinceguerra V (2002) Environmental toxins and breast cancer on Long Island. I. Polycyclic aromatic hydrocarbon DNA adducts. Cancer Epidemiol Biomarkers Prev 11(8): 677–685.
- Gammon MD, Sagiv SK, Eng SM, Shantakumar S, Gaudet MM, Teitelbaum SL, Britton JA, Terry MB, Wang LW, Wang Q, Stellman SD, Beyea J, Hatch M, Kabat GC, Wolff MS, Levin B, Neugut AI, Santella RM (2004) Polycyclic aromatic hydrocarbon-DNA adducts and breast cancer: a pooled analysis. Arch Environ Health 59(12): 640–649.
- Lee KH, Shu XO, Gao YT, Ji BT, Yang G, Blair A, Rothman N, Zheng W, Chow WH, Kang D (2010) Breast cancer and urinary biomarkers of polycyclic aromatic hydrocarbon and oxidative stress in the Shanghai Women's Health Study. Cancer Epidemiol Biomarkers Prev 19(3):877–883.
- Saieva C, Peluso M, Masala G, Munnia A, Ceroti M, Piro S, Sera F, Bendinelli B, Pala V, Sieri S, Tumino R, Giurdanella MC, Panico S, Mattiello A, Vineis P, Polidoro S, Matullo G, Palli D (2011) Bulky DNA adducts and breast cancer risk in the prospective EPIC-Italy study. Breast Cancer Res Treat 129(2): 477–484.
- Terry MB, Gammon MD, Zhang FF, Eng SM, Sagiv SK, Paykin AB, Wang Q, Hayes S, Teitelbaum SL, Neugut AI, Santella RM (2004) Polymorphism in the DNA repair gene XPD, polycyclic aromatic hydrocarbon-DNA adducts, cigarette smoking, and breast cancer risk. Cancer Epidemiol Biomarkers Prev 13(12): 2053–2058.
- Shantakumar S, Gammon MD, Eng SM, Sagiv SK, Gaudet MM, Teitelbaum SL, Britton JA, Terry MB, Paykin A, Young TL, Wang LW, Wang Q, Stellman SD, Beyea J, Hatch M, Camann D, Prokopczyk B, Kabat GC, Levin B, Neugut AI, Santella RM. Residential environmental exposures and other characteristics associated with detectable PAH-DNA adducts in peripheral mononuclear cells in a population-based sample of adult females. J Expo Anal Environ Epidemiol 2005;15:482–90.
- Perera F, Rundle A. Letter. Correspondence re: Gammon et al., Environmental Toxins and Breast Cancer on Long Island. I. Polycyclic Aromatic Hydrocarbon DNA Adducts. 11, 677–685, 2002 Cancer Epidemiol Biomarkers Prev. 12(1):75-6. 2003.
- Plíšková M, Vondráček J, Vojtěšek B, Kozubík A, Machala M. Deregulation of Cell Proliferation by Polycyclic Aromatic Hydrocarbons in Human Breast Carcinoma MCF-7 Cells Reflects Both Genotoxic and Nongenotoxic Events. Toxicological Sciences, Volume 83, Issue 2, 1 February 2005, Pages 246–256.
- Shen J, Liao Y, Hopper JL, Goldberg M, Santella RM, Terry MB. Dependence of cancer risk from environmental exposures on underlying genetic susceptibility: an illustration with polycyclic aromatic hydrocarbons and breast cancer. Br J Cancer. 2017 Apr 25;116(9):1229-1233.
- Korsh J, Shen A, Aliano K, Davenport T. Polycyclic Aromatic Hydrocarbons and Breast Cancer: A Review of the Literature. Breast Care 2015;10:316‑318.

Co-funded by the Health Programme of the European Union

EU funding disclaimer: This project has received funding from the 3rd European Union Health Programme 201-2020 under Grant Agreement PP-2-5-2016 (# 769767)

3.5. Perfluoroalkyl substances (PFASs, PFOS, PFOSA and PFOA)

Contaminants considered

The perfluoroalkyl substances (PFASs) are a family of perfluorinated chemicals that consist of a carbon backbone typically 4–14 in length and a charged functional moiety (primarily carboxylate, sulfonate, or phosphonate). The two most widely known PFASs contain an eight-carbon backbone and include perfluorooctanoic acid (PFOA) and perfluorooctane sulfate (PFOS) that are persistent compounds enduring for prolonged periods in the environment following the release and therefore some companies have foreseen the interruption of production and the replacement of PFOA and PFOS, changing production processes, reducing the release and level of these compounds in their products.

PFOA is used as a polymerization aid in the manufacture of several types of fluoropolymers, which have been used in a wide variety of industrial and consumer products, such as Teflon and Gore-Tex. PFOA does not break down in most environments.

Source

The PFAA have been used since the '50s in various industrial and commercial applications thanks to their chemical-physical characteristics (resist high temperatures, greases and water) as consumer products for fabrics, carpets and clothing, paper linings for food use, non-stick cookware and fire resistant foams.

Mean of exposure

PFOA, along with PFOS and other PFASs, have been detected in a variety of environmental matrices worldwide. These include surface water, air, mud, soils, sediments and polar ice caps. For example, PFOA and PFOS were detected in the Tennessee River downstream of a fluorochemical production facility, in drinking water sources near production facilities in West Virginia.

PFOS and PFOA are persistent in the environment and are found in human blood, breast milk and liver with a half-life of 4-10 years. PFOA has the potential for environmental long-range transport, which makes emissions of PFOA a transboundary pollution problem.

PFOA is found at low levels in the serum of most people living in the United States, with higher levels seen in professionally exposed workers. Sources of exposure in the general population are not well established, but they probably include diet, drinking water, food packaging and household products.

Co-funded by the Health Programme of the European Union

EU funding disclaimer: This project has received funding from the 3rd European Union Health Programme 201-2020 under Grant Agreement PP-2-5-2016 (# 769767)

Regulation and/or persistence

Besides PFOA also other substances in the PFASs group have properties of concern, which are targeted by the following international regulations: Perfluorinated carboxylic acids with a carbon chain of eleven to fourteen carbon atoms are also listed as substances of very high concern on the REACH candidate list because of their very persistent and very bioaccumulative properties. Perfluorooctane sulfonic acid (PFOS) is listed as persistent organic pollutant (POP) in Annex B of the Stockholm Convention. The U.S. EPA (Environmental Protection Agency) has established health advisories for two chemical contaminants called PFOA and PFOS based on the agency's assessment of the latest peer-reviewed science. EPA's assessment indicates that drinking water with individual or combined concentrations of PFOA and PFOS below 70 parts per trillion (0.07 micrograms per liter µg/L) is not expected to result in adverse health effects over a lifetime of exposure.

Evidence on (breast) cancer risk

While several studies report on the association between breast cancer and PCBs, only a few have investigated associations with the PFAAs, but for their potential for environmental persistence, their long human half-life, and possible toxicity, in the scientific community there is a rising concern because PFAAs might be associated with human cancers and for this reason it is necessary to continue scientific research linked to exposure to these types of persistent contaminants.

The recent case-control study **[Wielsoe 2017]** on Inuit women from Greenland found significant, positive associations between breast cancer risk and PFAAs were observed.

The participants were asked to complete a questionnaire with information on reproductive history and lifestyle and to provide a blood sample. The serum levels of different persistent contaminants, among which 16 perfluoroalkyl acids (PFAAs), were determined.

Positive associations between breast cancer risk and PFOA was found in 2nd tertile of serum (ng/ml) levels (OR=1.26, 95% CI 1.01-1.58) and in 3rd tertile (OR=2.64, 95% CI 1.17-5.97).

The associations indicate that environmental exposure to PFOA can be a factor increasing the risk for breast cancer in Inuit women.

IARC Monography

The International Agency for Research on Cancer (IARC) in the Monograph on the evaluation of carcinogenic risk to humans "Some chemicals used as solvents and in polymer manufacture." Vol. 110 (2016) carried out an evaluation to investigate the association between PFOA exposure and cancer in humans. The results showed limited evidence of the carcinogenicity of PFOA and a positive association with cancers of the testes and kidney. IARC has classified PFOA as possibly carcinogenic to humans (Group 2B). Few population-based case-control studies were available that examined PFOA serum concentrations in relation to various types of cancer, in particular breast cancer.

Co-funded by the Health Programme of the European Union

EU funding disclaimer: This project has received funding from the 3rd European Union Health Programme 201-2020 under Grant Agreement PP-2-5-2016 (# 769767)

Drinking-water is thought to have been the predominant source of intake of PFOA for a highly exposed population near a production facility in West Virginia, USA, studied by the C8 Science Panel **[Barry 2013; Vieira 2013]** where both surface water and groundwater were contaminated by water and air emissions from the facility.

[Barry 2013] examined incident cancers occurring in 1992–2011 through the state cancer registries or medical record review. The total sample size was 32.254, of whom 3713 (11.5%) had worked at some time in the production plant. Individual-level data on residential history, drinking-water source, and tap-water consumption were obtained from the questionnaires administered in 2005–2011 in a cohort identified as a result of a lawsuit brought by residents of the area surrounding the fluoropolymer production plant in West Virginia. PFOA exposure was associated with kidney and testicular cancer in this population but for breast cancer there is no association between exposure to cumulative PFOA serum concentration (RR=0.93, 95% CI 0.88–0.99).

Using a case‑control design **[Vieira 2013]** examined incident cancers occurring in 1996‑2005, using West Virginia and Ohio state cancer registries. Cases living in 13 counties around the fluoropolymer production plant were identified; analyses were limited to 18 cancer types that were of a-priori interest, or that had at least 100 cases in each state. The controls for each analysis were all other cancer types, excluding cancers of the kidney, liver, pancreas, and testes. In one set of analyses, residence at time of diagnosis was used to assign study participants to specific water districts in Ohio and West Virginia. Breast cancer was no associated with PFOA serum concentrations (µg/l) in all different category (low to very high) compared with cases living in unexposed areas.

A case-control study in Greenland **[Bonefeld-Jorgensen 2011]** examined risk of cancer of the breast in relation to PFOS and PFSA exposure and found an association between breast cancer and PFOS (OR=1.03, 95% CI 1.001-1.07) and ΣPFSA (OR=1.03, 95% CI 1.00-1.05).

This case control study is very small (31 cases and 115 controls of incident cases of cancer of the breast in Greenland in 2002‑2003) and for the working group of the IARC is uninformative because of the small sample size resulting from the high proportion of missing covariate data.

A later prospective Danish study **[Bonefeld-Jorgensen 2014]** evaluates the association between serum levels of PFAS in pregnant Danish women and the risk of premenopausal BC during a follow-up period of 10–15 years. An increased risk for the highest perfluorooctane sulfonamide (PFOSA) was found by a logistic regression analyses of the quintiles and the association with breast cancer showed a stronger significant correlation for PFOSA in the 5th quintile (RR=2.40, 95% CI 1.20-4.83) where the association is strongest among the young women below fourty years of age, but the overall results of this study suggest no strong or coherent association between breast cancer occurrence and the measured PFAS.

Co-funded by the Health Programme of the European Union

EU funding disclaimer: This project has received funding from the 3rd European Union Health Programme 201-2020 under Grant Agreement PP-2-5-2016 (# 769767)

Another recent case-control study **[Ghisari 2014]** is based on environmental exposure to POPs including PFAS and breast cancer risk in inuit Greenlandic women and has studied the main effect of polymorphisms in genes involved in xenobiotic metabolism and in the biosynthesis of estrogens, CYP1A1, CYP1B1, COMT and CYP17, CYP19 and the BRCA1 founder mutation in relation to the risk of BC and to explore possible interactions between gene polymorphisms and serum PFASs levels on BC risk in greenland inuit women. The mutation and polymorphisms of BRCA1 founder in CYP1A1 (Val) and CYP17 (A1) may increase the risk of BC among Inuit women and the risk increases with higher serum PFOS and PFOA levels.

Reviews

The review of human PFOA exposure studies **[Steenland 2010]** is limited to assessing occupational exposure to US labor cohorts. In this review regarding the occupational exposure to PFOA for breast cancer no excess of breast cancer is recorded.

In addition, a more recent review **[Siddique 2016]** also takes up the case-control study on women coming from Greenland **[Bonefeld-Jorgensen 2011]** where, as we saw in the previous paragraph, the risk of breast cancer was found to be associated with the serum level both for PFOS and for the sum of PFSA, before and after adjustment for the confounding factors.

References Polycyclic PFAS

- Barry V, Winquist A, Steenland K (2013). Perfluorooctanoic acid (PFOA) exposures and incident cancers among adults living near a chemical plant. Environ Health Perspect, 121(11-12):1313‑8.
- Bonefeld-Jorgensen EC, Long M, Bossi R, Ayotte P, Asmund G, Kruger T, et al. (2011). Perfluorinated compounds are related to breast cancer risk in Greenlandic Inuit: a case control study. Environ Health, 10(1):88.
- Bonefeld-Jorgensen EC, et al. Breast cancer risk after exposure to perfluorinated compounds in Danish women: a case-control study nested in the Danish National Birth Cohort. Cancer Causes Control. 2014;25(11):1439‑48
- Vieira VM, Hoffman K, Shin HM, Weinberg JM, Webster TF, Fletcher T (2013b). Perfluorooctanoic acid exposure and cancer outcomes in a contaminated community: a geographic analysis. Environ Health Perspect, 121(3):318‑23. doi:10.1289/ehp.1205829 PMID:23308854
- Wielsoe M, Kern P and Bonefeld-Jørgensen CB. Serum levels of environmental pollutants is a risk factor for breast cancer in Inuit: a case control study. Environmental Health (2017) 16:56
- IARC (2016). Some chemicals used as solvents and in polymer manufacture. Volume 110. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. Lyon: International Agency for Research on Cancer; 2016
- Ghisari M, Long M, Bonefeld-Jorgensen EC. Genetic polymorphisms in CYP1A1, CYP1B1 and COMT genes in Greenlandic Inuit and Europeans. Int J Circumpolar Health. 2013;72:211-13.
- Steenland K, Fletcher T, and Savitz DA. Epidemiologic Evidence on the Health Effects of Perfluorooctanoic Acid (PFOA). EHP, Vol. 118, N°8, 2010
- Siddique S, Kubwabo C, Harris SA. A review of the role of emerging environmental contaminants in the development of breast cancer in women. Emerging Contaminants 2 (2016) 204-219.
- https://ntp.niehs.nih.gov/ntp/ohat/pfoa_pfos/pfoa_pfosmonograph_508.pdf
- https://www.epa.gov/ground-water-and-drinking-water/drinking-water-health-advisories-pfoa-and-pfos

Co-funded by the Health Programme of the European Union

EU funding disclaimer: This project has received funding from the 3rd European Union Health Programme 201-2020 under Grant Agreement PP-2-5-2016 (# 769767)

3.6. Triazine (atrazine, simazine, terbuthylazine and metabolites desethyl-atrazine, desethyl-terbuthylazine)

Contaminants considered

Triazine herbicides atrazine, simazine, terbuthylazine and desetyl-atrazine metabolites, desethyl-terbuthylazine are among the most widespread substances in the many years of investigations, both in surface and underground waters, with concentrations that often exceed the limit of 0.1 µg/l set for drinking water. Atrazine is used in agriculture as a selective pre and post-emergence herbicide for annual control of grass and broad-leaved weeds. It has been used on asparagus, bananas, citrus groves, coffee, conifers, forestry, orchards, prairies, herbaceous crops, guavas, macadamia orchards, corn (maize), oil palms, sorghum, sugar cane, pineapples, roses and screws. It has also been used as a soil sterilizer for airfields, parking lots and industrial sites and as an algaecide in swimming pools. Recently, many of the uses that contribute to water waste have been reduced or eliminated. In the European Union, where a limit of 0.1 µg/l has been set for all pesticide residues in drinking water and groundwater, the use of atrazine-containing herbicides has been limited mainly to agricultural uses on maize and on the sorghum.

Source

The continued use of atrazine as a primary herbicide for years has led to the contamination of aquifers and soil with it because atrazine is one of the most used herbicides with 76 million pounds applied every year as it is cheap and effective.

Mean of exposure

Atrazine is applied to agricultural fields or crops to kill weeds. It is also used near highways and railways for the same purposes. Some atrazines can enter the air after being applied to the ground. Some atrazines can also be washed from the ground due to rainfall and enter the surrounding areas, including streams, lakes or other watercourses. Some atrazines can migrate from the upper soil surface to deeper layers of the soil and enter the groundwater. People living near areas where atrazine has been applied to crops can be exposed through contaminated drinking water. Atrazine has been found in about 20 Superfund sites in the United States. People living near these sites may be exposed to higher levels of atrazine. If you are a worker working with atrazine, you may be exposed to higher amounts of atrazine. The government estimated that around thousand people could be exposed to atrazine in this way. Atrazine, one of the most widely used herbicides in the United States, is intentionally applied to crops, in particular corn, sugar cane, pineapple and sorghum. Therefore, people living near the areas where these crops are grown, especially agricultural workers and herbicide applicators applying atrazine, may be exposed to atrazine because it is used in agriculture.

Co-funded by the Health Programme of the European Union

EU funding disclaimer: This project has received funding from the 3rd European Union Health Programme 201-2020 under Grant Agreement PP-2-5-2016 (# 769767)

You may be exposed to atrazine if you are in the vicinity when the cultures are treated with atrazine, if you are involved in the application of atrazine in crops, or if you are close to other places where it is applied. Most often, atrazine is not found in high concentrations in the air, but can be found in higher concentrations in near-air facilities or in areas where it is applied to crops. You could also be exposed to atrazine by digging in the dirt that contains atrazine.

Children may be exposed to atrazine by playing in the dirt containing atrazine. You and your children may be exposed to atrazine if you drink water from wells contaminated with the herbicide. While it is used on many crops, it has not been found in many food samples and therefore only at very low levels. Therefore, it is very unlikely that it would be exposed to atrazine by eating foods.

Regulation and/or persistence

Atrazine was banned in the European Union in 2005 due to persistent contamination of groundwater caused by it and studies indicating its carcinogenic potential for mammary gland, prostate gland and also its correlation with ecological interruptions.

Other federal agencies that develop regulations for toxic triazine substances are the Environmental Protection Agency (EPA), the Occupational Safety and Health Administration (OSHA), the Food and Drug Administration (FDA), the Agency for Toxic Substances and the Register of diseases (ATSDR) and the National Institute for Occupational Safety and Health (NIOSH). Regulations and recommendations may be expressed in levels not to be exceeded in air, water, soil or food that are usually based on levels that affect animals; so they are regulated to help protect people.

Atrazine is currently under review for the re-registration of pesticides by the EPA. Therefore, the EPA can be contacted for more information on atrazine. OSHA has set a limit of 5 mg atrazine/m³ of laboratory air for an 8-hour working day. NIOSH recommends a standard for occupational exposure of 5 mg atrazine/m³ of laboratory air during a 10-hour shift to protect workers from a concern that atrazine may cause cancer. The EPA has set a maximum allowable amount of atrazine in drinking water of 3 µg/l. In addition, atrazine is designated as a limited-use pesticide, which means that only certified pesticide applicators can use atrazine.

Evidence on (breast) cancer risk

Atrazine is a known endocrine disruptor. It interferes with the pituitary-ovarian axis by decreasing the levels of prolactin and luteinization, changes that contribute to increase the cancer of the mammary gland. There is documented evidence of atrazine that causes dramatic damage to the reproductive structures of frogs, fish and other wildlife. Atrazine also induces an increased activity of the aromatase enzyme which causes an increase in estrogen levels that is directly linked to breast cancer. Epidemiological studies do not provide any support for a causal relationship between atrazine exposure and breast cancer, if triazine herbicides cause cancer in humans it is still a matter of debate.

Co-funded by the Health Programme of the European Union

EU funding disclaimer: This project has received funding from the 3rd European Union Health Programme 201-2020 under Grant Agreement PP-2-5-2016 (# 769767)

IARC Monography

The International Agency for Research on Cancer in the Monograph on the evaluation of carcinogenic risk to humans of Atrazine in the Vol. 73 (1999) downgraded atrazine from group 2B (possibly carcinogenic to humans) to group 3 (not classifiable with regard to its carcinogenicity to humans). The Working Group concluded that the animal mammary cancers associated with exposure to atrazine involve a non-DNA-reactive, hormonally mediated mechanism that is not relevant to humans.

Reviews

The purpose of the review **[Boffetta 2013]** was to critically review several epidemiologic population-based studies on atrazine exposure and the risk of cancer including breast cancer and to compare these studies with the conclusions of the Environmental Protection Agency and the scientific panel on the carcinogenicity of atrazine, to determine whether epidemiological studies support a causal relationship between atrazine and any specific cancer.
The EPA considered seven epidemiological studies including four ecological studies, two case-control studies and the potential agricultural health study (AHS).

According to the review of **[Boffetta 2013]**, four ecological studies have provided inconsistent and weak evidence of an association between atrazine and breast cancer **[Kettles 1997; Hopenhayn-Rich 2002; Muir 2004; Mills and Yang, 2006];** the only case-control study that found an association is that of **[Kettles 1997],** although the results in a better-designed follow-up study **[Hopenhayn-Rich 2002]** have not been replicated.

The Kentucky Environmental Study **[Kettles 1997]** evaluated triazine exposure and breast cancer incidence in Kentucky counties classified as having low, medium or high triazine exposure based on triazine concentration in groundwater from 1990 to 1991 and in surface waters from 1993 to 1994; for the hectares of wheat planted in 1970, 1980 and 1990; and for the total use of pesticides in 1979 in that area.
Breast cancer incidence rates for each county for the years 1991-1994 were obtained from the state registry. An OR of 1.14 (95% CI 1.08-19.10) and 1.20 (95% CI 1.13-1.28) was reported for mean and high levels of triazine exposure, respectively, for period 1993-1994.

This other important ecological study **[Hopenhayn-Rich 2002]** is an expansion of a previous investigation conducted in Kentucky **[Kettles 1997]** that have evaluated the association between atrazine exposure and breast cancer for the period 1993–1997 using the same methods.
On the basis of breast cancer incidence rates from the state registry for 1993–1997, there was no association between breast cancer and atrazine exposure. The OR 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.

Co-funded by the Health Programme of the European Union

EU funding disclaimer: This project has received funding from the 3rd European Union Health Programme 201-2020 under Grant Agreement PP-2-5-2016 (# 769767)

The ecological study in UK **[Muir 2004]** examined the distribution of breast cancer incidence and atrazine data in two agricultural counties with a high incidence of breast cancer (Lincolnshire and Leicestershire) to examine spatial clustering that might suggest a common exposure. Using a linear regression analysis to examine the spatial association between incidence of breast cancer and atrazine, the use of atrazine was not significantly associated with breast cancer, nor there was any association between urban electoral departments in both provinces.

In this large study focused on an agricultural population **[Mills and Yang 2006],** where 23,513 breast cancer cases were analyzed, the authors' confidence in the results was reinforced by significant associations for established breast cancer risk factors.
The researchers evaluated the association between breast cancer rate data between the Latin Cancer Registry and the data on atrazine pounds applied by the California Pesticide Regulatory Department. For the highest group of atrazine use, the adjusted RR was 0.87 (95% CI 0.73-1.04) without dose-response relationship. No association between breast cancer incidence and atrazine data was found even in the ecological study of Latinas carrying out agricultural work in California.

Both the population-based case-control study in a high-use area of atrazine in Wisconsin and in North Carolina (AHS) **[McElroy 2007; Engel 2005]** found no association with breast cancer.

[McElroy 2007] used data from three case-control studies of chemical agricultural monitoring on breast cancer in rural Wisconsin, atrazine exposure values were assigned retrospectively to study participants. Exposure to atrazine was estimated using a weighted moving average on groundwater well data to calculate an interpolated value assigned to each individual; it emerges that there is no association between atrazine exposure and breast carcinoma (OR=1.1, 95% CI 0.9-1.5 for levels 1.0-2.9 ppb; OR=1.3, 95% CI 0.3-5.0 for levels above 3.0 ppb).

[Engel 2005] assessed the relationship between potential pesticide exposure and incidence of breast cancer among farmers, because the assessment of exposure to atrazine was less detailed in farmers' wives than in their husbands, so exposure data of husbands have been used as an indirect measure of wives' exposure. After adjustment for potential confounders, breast cancer was not associated with atrazine, based on the use of the wife (RR=0.7, 95% CI 0.4-1.2) or the use of the husband (RR=1.1, 95% CI 0.7-1.6), or for all cases of breast cancer or postmenopausal breast cancer (RR=0.4, 95% CI 0.1-1.0 for wife's exposure and RR=1.0, 95% CI 0.6-1.7 for husband's exposure).

Co-funded by the Health Programme of the European Union

EU funding disclaimer: This project has received funding from the 3rd European Union Health Programme 201-2020 under Grant Agreement PP-2-5-2016 (# 769767)

Also the cohort study of Iowa and North Carolina **[Beane Freeman 2011]** found no significant association between atrazine use and breast cancer according to nine exposed and 27 unexposed cases (RR=1.14, 95% CI 0.47-2.50) and no evidence of an increased risk for those above the median level of lifetime days of use.
Overall, the EPA considered both epidemiological and toxicological data to determine that "the database lacks evidence of an association between atrazine and breast cancer".

Also in the reviews of scientific literature exerted by **[Simpkins 2011; Sathiakumar 2011],** it can be seen that the conclusions are the same found in the most recent revision of **[Boffetta 2013]** and that there is no epidemiological evidence suggesting that exposure to atrazine is directly associated at the onset of breast cancer in women and to date there is still a lack of a plausible mode of action for the onset of breast cancer linked to exposure of atrazine in women.

References Triazine

- Kettles MK, Browning SR, Prince TS, Horstman SW (1997). Triazine herbicide exposure and breast cancer incidence: an ecologic study of Kentucky counties. Environ Health Perspect 105:1222–1227.
- McElroy JA, Gangnon RE, Newcomb PA, Kanarek MS, Anderson HA, Brook JV, et al. (2007). Risk of breast cancer for women living in rural areas from adult exposure to atrazine from well water in Wisconsin. J Expo Sci Environ Epidemiol 17:207–214.
- Beane Freeman L, Rusiecki JA, Hoppin JA, Lubin JH, Koutros S, Andreotti G, et al. (2011). Atrazine and cancer incidence among pesticide applicators in the Agricultural Health Study (1994–2007). Environ Health Persp 119:1253–1259.
- Engel LS, Hill DA, Hoppin JA, Lubin JH, Lynch CF, Pierce J, et al. (2005). Pesticide use and breast cancer risk among farmers' wives in the Agricultural Health Study. Am J Epidemiol 161:121–135.
- Hopenhayn-Rich C, Stump ML, Browning SR (2002). Regional assessment of atrazine exposure and incidence of breast and ovarian cancers in Kentucky. Arch Environ Contam Toxicol 42:127–136.
- Mills PK, Yang R (2006). Regression analysis of pesticide use and breast cancer incidence in California Latinas. J Environ Health 68:15–22.
- Muir K, Rattanamongkolgul S, Smallman-Raynor M, Thomas M, Downer S, Jenkinson C (2004). Breast cancer incidence and its possible spatial association with pesticide application in two counties of England. Public Health 118:513–520.
- Boffetta P, Adami HO, Berry C and Mandel JS. Atrazine and cancer: a review of the epidemiologic evidence European Journal of Cancer Prevention 2013, Vol 22 No 2
- Simpkins JW, Swenberg JA, Weiss N, Brusick D, Eldridge JC, Stevens JT, Handa RJ, Hovey RC, Plant TM, Pastoor TP, Breckenridge CB. Atrazine and Breast Cancer: A Framework Assessment of the Toxicological and Epidemiological Evidence Toxicol Sci. Oct;123(2):441-59. 2011.
- Sathiakumar, N., MacLennan, P. A., Mandel, J., and Delzell, E. A review of the epidemiologic studies of triazine herbicides and cancer. Crit. Reviews Toxicol. 41(Suppl. 1), 1–34. 2011.
- IARC (1999). Monographs on the evaluation of carcinogenic risks to humans. Evaluation and re-evaluation of some agents which target specific organs in rodent bioassays. 73: Lyon: IARC; pp. 59–113.

Co-funded by the Health Programme of the European Union

EU funding disclaimer: This project has received funding from the 3rd European Union Health Programme 201-2020 under Grant Agreement PP-2-5-2016 (# 769767)

3.7 – Cadmium (heavy metal)

Contaminants considered

Cadmium is a non-essential metal that is naturally present in the environment, even in the most pristine or remote ones. With current analytical facilities, it is well detectable in almost any environmental samples, e.g. rocks, soils, surface and rain water, plants and humans. The concentrations of Cd are typically in the parts per billion or parts per trillion (mass based parts) concentration range, i.e. trace levels. Older environmental concentration data always need to be treated with caution but currently there are numerous data to reliably identify Cd occurrence in the environment.

Source

Over 90% of the Cd in the surface environment comes from anthropogenic sources, including rock phosphate fertilizers, fossil fuel combustion ash, cement production waste, metallurgical works, municipal waste, sewage sludge and atmospheric deposition.

The main sources of non-occupational cadmium exposure in the general population include smoke, air, food and water contaminated with cadmium. Cadmium is also found naturally in natural phosphate, the main material used for mineral phosphate fertilizers (P). The long-term use of mineral fertilizers P has enriched the agricultural land with Cd.

Mean of exposure

Cadmium occurs in the environment as a divalent cation that can be absorbed by the biota. This means that this element can be transferred from soil and water to human food chains, with generally greater importance of terrestrial parts (food crops) than the aquatic environment (fish) in the human diet.

The evidence also indicates that the increase in total Cd concentrations of soil due to atmospheric deposition or use of phosphate fertilizers is associated with an almost proportional increase in Cd concentrations of crops, all other factors being constant. Cd smoke and diet are the main ways of exposure to Cd in pristine areas. Tobacco plants naturally contain high concentrations of Cd in the leaves, the amount of which varies considerably with the origin of the tobacco. Although cadmium is only one constituent of tobacco smoke, smoking does increase body cadmium burden **[Darbre 2006].** Food intake is the main source of Cd exposure for the general non-smoking population.

The levels of Cd in foods are typically high in offal, organs, equine products, crustaceans, cocoa, mushrooms and some green leafy vegetables. The incidence of these products in the average intake of Cd in the diet is low due to their low average consumption. In contrast, concentrations of Cd of cereals and potatoes have received considerable attention due to their greater impact on the intake of Cd by humans.

Co-funded by the Health Programme of the European Union

EU funding disclaimer: This project has received funding from the 3rd European Union Health Programme 201-2020 under Grant Agreement PP-2-5-2016 (# 769767)

Both the natural and anthropogenic sources of cadmium, including industrial emissions and the application of fertilizers and sewage sludge to agricultural land, can lead to soil contamination and the increase of cadmium by crops and vegetables grown for the human consumption.

Cadmium transported from the air will also add the cadmium content in wild plants, berries, fungi and wild animals, which together add to oral human exposure. Although the emission of cadmium from point sources has decreased in recent years, there are still considerable quantities of cadmium in various products and constructions. This cadmium may eventually enter the human route of exposure.

The process of soil cadmium absorption by plants has improved at low pH, therefore, the decrease in soil pH due to environmental acidification, a recognized problem in Sweden, can further increase the cadmium content in the human exposure route.

When assessing human exposure to environmental cadmium, it is important to consider all routes of exposure, as well as factors affecting the level of exposure and dose, for example, lifestyle factors such as smoking, food consumption and nutritional factors which can influence the absorption of cadmium. Smoking is an important source of cadmium exposure.

Regulation and/or persistence

Classification and workplace exposure limits set by the American Conference of Governmental Industrial Hygienists for Cadmium are: A2 (substances suspected of being carcinogenic to humans), respirable fraction, TWA 0.002 mg/m³. While the exposure limit value established by the Occupational and Safety Health Administration (OSHA) is: 0.1 mg/m³.

Evidence on (breast) cancer risk

Recently, cadmium has been shown to be a chemical that destroys the endocrine system with estrogenic properties and a potential carcinogen of the prostate. In addition to being persistent and toxic, Cd is bioaccumulative with high concentrations occurring mainly in the kidney. The carcinogenic effects of cadmium on the prostate and breast in rats were probably due to the estrogenic properties of the heavy metal that allowed it to bind to the cellular estrogen receptors and thus imitate the actions of estrogen.

Two case–control studies **[McElroy 2006; Gallagher 2010]** have directly examined the association between urinary cadmium and breast cancer risk in US women by observing a significant trend in increased risk of breast cancer from elevated levels of urinary cadmium that also is independent of tobacco use; although smoking is a well-established source of cadmium exposure, the main route of cadmium exposure is food ingestion, in particular root vegetables. **[Gallagher 2010].**

Co-funded by the Health Programme of the European Union

EU funding disclaimer: This project has received funding from the 3rd European Union Health Programme 201-2020 under Grant Agreement PP-2-5-2016 (# 769767)

Another recent study in Lithuania **[Strumylaite 2011]** aimed to determine and compare the concentration of cadmium (Cd) in various biological media (breast tissue, urine and blood) of breast cancer and benign breast cancer patients. Women reported that the average cadmium levels in breast and urine tissue were significantly higher in breast cancer patients. Cancer patients with estrogen positive (ER) receptors had a significantly higher Cd concentration of breast tissue compared to patients with ER negative **[Strumylaite 2011].**

In Japan, exposure to environmental cadmium is relatively higher, even in non-polluted areas, than in other countries; in a recent case-control study in Japan **[Nagata 2013]** have found that a higher urinary cadmium level was associated with an increased risk of breast cancer among Japanese women. Women in the middle and highest tertiles of urinary cadmium levels showed significantly elevated OR of breast cancer relative to those in the lowest tertile; furthermore the trend of increased risk with increasing cadmium level was also statistically significant; urinary cadmium per 1.0 µg/g of creatinine increment was associated with an OR of 1.67 (95 % CI 1.39-2.01).

IARC Monography

The International Agency for Research on Cancer (IARC) in the Monograph on the evaluation of carcinogenic risk to humans in the Vol. 58 (1993) regarding possible causal associations between cadmium exposures and human cancers, reviewed and evaluated the available epidemiologic findings and other relevant information on cadmium exposures and concluded there was sufficient evidence in humans for the carcinogenicity of cadmium and cadmium compounds. So, cadmium has classified as a carcinogen for humans (group I) by the International Agency for Research on Cancer (IARC) on the basis of occupational studies of nickel-cadmium manufacturing, cadmium processing, cadmium-recovery plants, and copper-cadmium alloy plants. Most studies reported excess mortality from lung cancer among cadmium-exposed workers. There are very few case control and/or cohort studies correlating the exposure to cadmium and the risk of breast cancer, the most interesting case-control study for the size of the population is that of McElroy et al. 2006 described in detail in the previous paragraph.

Reviews

In the review of **[Jarup 1998]** diet is the main source of cadmium exposure in the general Swedish non-smokers population. The average daily intake is around 15 µg/day, but there are large individual variations due to differences in energy intake and eating habits**.**

Some recent studies indicate an association between cadmium exposure and human breast cancer, and it has been suggested that the effects of cadmium are mediated by the estrogen receptor independent of estradiol **[Morales 1994]**.

Co-funded by the Health Programme of the European Union

EU funding disclaimer: This project has received funding from the 3rd European Union Health Programme 201-2020 under Grant Agreement PP-2-5-2016 (# 769767)

A Finnish case–control study **[Antila 1996]** unexpectedly detected high concentrations of cadmium in breast tissue samples, which may indicate that cadmium-binding proteins exist in human breast tissue. The correlation of cadmium with estrogen receptors in breast cancer was suggestive. The authors cautioned that their results neither demonstrated nor denied the role of initiation, promotion or progression of cadmium in breast cancer. The cadmium concentrations found in the breast cancer patients did not differ statistically significantly from those of the healthy controls.

References Cadmium

- McElroy JA, Shafer MM, Trentham-Dietz A, Hampton JM, New comb PA (2006) Cadmium exposure and breast cancer risk. J Natl Cancer Inst 98:869–872.
- Gallagher CM, Chen JJ, Kovach JS (2010) Environmental cadmium and breast cancer risk. Aging 2:04–814.
- Strumylaite L, Bogusevicius A, Abdrachmanovas O, Baranauskiene D, Kregzdyte R, Pranys D, Poskiene L (2011) Cadmium concentration in biological media of breast cancer patients. Breast Cancer Res Treat 125:511–517.
- Pan J, Plant JA, Voulvoulis N, Oates CJ, Ihlenfeld C. Cadmium levels in Europe: implications for human health. Environ Geochem Health. 2010 Feb;32(1):1-12.
- Morales PG, Saceda M, Kenney N, Kim N, Salomon DS, Gottardis MM, Solomon HB, Sholler PF, Jordan VC and Martin MB. Effect of cadmium on estrogen receptor levels and estrogen-induced responses in human breast cancer cells. J Biol Chem. 1994;269(24):16896-901.
- Nagata C, Nagao Y, Nakamura K, Wada K, Tamai Y, Tsuji M, Yamamoto S, Kashiki Y. Cadmium exposure and the risk of breast cancer in Japanese women. Breast Cancer Res Treat (2013) 138:235–239.
- Jarup L, Berglund M, Elinder CG, Nordberg G, Vahter M. Health effects of cadmium exposure--a review of the literature and a risk estimate. Scand J Work Environ Health. 1998;24 Suppl 1:1-51.
- IARC (1993). Cadmium and cadmium compounds. In: Beryllium, cadmium, mercury and exposure in the glass manufacturing industry. Lyon: IARC, 1993: 119-237. IARC monographs on the evaluation of carcinogenic risks to humans, vol 58.
- World Health Organization (WHO). Cadmium. Geneva: WHO, 1992. Environmental health criteria, vol 134.
- World Health Organization (WHO). Cadmium. Geneva: WHO, 1992. Environmental health criteria, vol 135.
- Antila E , Mussalo-Rauhamaa H , Kantola M , Atroshi F , Westermarck T Association of cadmium with human breast cancer. The Science of the Total Environment [01 Jul 1996, 186(3):251-256]
- Darbre PD, Metalloestrogens: an emerging class of inorganic xenoestrogens with potential to add to the oestrogenic burden of the human breast. J. Appl. Toxicol. 2006; 26: 191–197

Co-funded by the Health Programme of the European Union

EU funding disclaimer: This project has received funding from the 3rd European Union Health Programme 201-2020 under Grant Agreement PP-2-5-2016 (# 769767)

3.8. Trihalomethanes (THMs) (bromoform, bromo-dichloro-methane, dibromochloromethane, chloroform)

Contaminants considered

Trialomethane is a compound in which three hydrogen atoms of the methane molecule (CH4) are substituted with atoms of one or more halogens. If the three hydrogens are replaced with three atoms of the same halogen, then the compound is called haloform: chloroform (CHCl3), bromoform (CHBr3), iodoform (CHI3), fluoroform (CHF3).

Bromo-trihalomethanes are used as laboratory reagents, in the synthesis of organic compounds, as solvents. Bromoform has been used as a cough sedative. Chloroform is used in production of refrigerants and as a solvent; it was used in the past as an anesthetic. The main trihalomethanes are represented by chloroform, bromodichloromethane, dibromochloromethane, bromoform.

Source

Trihalomethanes (THM) are formed in drinking water mainly due to the chlorination of organic matter naturally present in raw water stocks but they are also found as pollutants introduced as such and then dispersed into the environment. The speed and the degree of formation of THM increase as a function of the concentration of chlorine and humic acid, temperature, pH and concentration of bromide ions.

Chloroform is the most common THM and the main DBP (disinfection by-products) in chlorinated drinking water. In the presence of bromides, the brominated THM are preferentially formed and the chloroform concentrations decrease proportionally. It is assumed that most of the THMs present in the water are eventually transferred into the air due to their volatility. For chloroform, for example, individuals may be exposed to high concentrations of chlorinated tap water during the shower. In Italy for example, the decree law D.L. 31/2001 imposes the limit of 30 µg / l for the sum of THM (more restrictive than the EU) for human consumption waters.

Mean of exposure

For volatile THMs, approximately equal contributions to total exposure come from four areas: drinking water ingestion; indoor air inhalation largely due to volatilisation from drinking water; inhalation and cutaneous exposure during showering or bathing; food ingestion; with everything except food exposure resulting mainly from drinking water. The exposure of indoor air to volatile THM is particularly important in countries with low rates of ventilation in homes and high rates of showering and bathing.

Co-funded by the Health Programme of the European Union

EU funding disclaimer: This project has received funding from the 3rd European Union Health Programme 201-2020 under Grant Agreement PP-2-5-2016 (# 769767)

Four trihalomethanes (clloform, IARC 2B group), bromodichloromethane (IARC 2B group), dibromochloromethane (IARC group 3) and bromoform (IARC group 3), together with nine haloacetic acids based on bromine and chlorine, are the main by-products of chlorination on weight basis. The most recent studies quantified the exposure to trihalomethanes as a proxy for the whole mixture.

Regulation and/or persistence

The most prevalent DBP in drinking water are trihalomethanes (THM), which are the only DBP group regulated in the EU with a maximum contaminant level of 100 µg/l. Several DBPs have been shown to be genotoxic in vitro assays and carcinogenic in animal experiments and the WHO International Agency for Research on Cancer (IARC) classifies chloroform and other widespread DBP as possible human carcinogens.

Evidence on (breast) cancer risk

Some studies indicate that chlorinated by-products in drinking water (e.g. chloroform) may contribute slightly to the risk of breast cancer, which is the basis for a possible correlation between some DBPs in drinking water and breast cancer. Among the few epidemiological studies on the exposure to DBP and BC, some have found a positive association **[Ribera 2018]**.

However, most of the studies concerning the effects of THMS on breast cancer show a negative correlation. For example**, [Marcus 1998]** conducted an ecological study that describes the association between the total levels of trihalomethane in water provided publicly and the incidence of female invasive breast cancer. Total trihalomethane levels were not materially associated with breast cancer risk, adapting to potential confounders. When stratified by race, the association observed for the aforementioned total trihalomethane category was not very different in black women than in white women. These ecological data are compatible with untreated or weak-treated trihalomethanes in drinking water related to breast cancer risk.

The retrospective cohort study **[Vinceti 2004]** conducted in northern Italy (Guastalla) is very interesting: they have studied the mortality of a cohort to which tap water was supplied with high chloroform and trihalomethane. In this study the risks of breast, ovarian and prostate cancer also tend to increase in subjects with higher socio-economic status, so the excess rates found in our exposed cohort cannot easily be attributed to life.

Co-funded by the Health Programme of the European Union

EU funding disclaimer: This project has received funding from the 3rd European Union Health Programme 201-2020 under Grant Agreement PP-2-5-2016 (# 769767)

IARC Monography

Association between the ingestion of chlorinated drinking water in excess with risk of cancer followed by mortality has been reported in several epidemiological studies in the IARC Monograph on the Evaluation of Carcinogenic Risk to Human “Chlorinated Drinking Water, Chloroform By-product, Some Other Halogenated Compound Cobalt and Cobalt Compound”, Vol. 52 Lyon IARC, 1991 and in the “Monographs on the evaluation of some chemicals present in industrial and consumer products food and drinking-water” in the Vol. 101 (2013).

[Doyle 1997] conducted a study among women only and found a significantly increased risk and a dose-response relationship with levels of chloroform for all cancers included breast cancer.
In a cohort study in Finland **[Koivusalo 1997]** an excess risk of breast cancer (RR=1.33, 95% CI 1.02-1.74) was also observed in relation to surface water use; they have also identified a significantly increased risk among women for cancers of the urinary bladder, colon, oesophagus and breast with increasing mutagenicity of the water.

Reviews

In the review of **[Mohamadshafiee 2012]** some studies indicate that chlorination by-products in drinking water may slightly contribute to the risk of breast cancer; however, most of the studies concerning the effects of THMS on breast cancer show a negative correlation.

References Trihalomethanes

- Vinceti M, Fantuzzi G, Monici L, Cassinadri M, Predieri G, Aggazzotti G, 2004. A retrospective cohort study of trihalomethane exposure through drinking water and cancer mortality in northern Italy. Sci. Total Environ. 330, 47–53.
- Doyle TJ, Zheng W, Cerhan JR, Hong CP, Sellers TA, Kushi LH et al., 1997. The association of drinking water source and chlorination by-products with cancer incidence among postmenopausal women in Iowa: a prospective cohort study. Am. J. Public Health 87, 1168–1176.
- Koivusalo M, Pukkala E, Vartiainen T, Jaakkola JJ, Hakulinen T. 1997. Drinking water chlorination and cancer: a historical cohort study in Finland. Cancer Causes Control 8, 192–200.
- Marcus PM, Savitz DA, Millikan RC, Morgenstern H, 1998. Female breast cancer and trihalomethane levels in drinking water in North Carolina. Epidemiology 9, 156–160.
- Ribera FL, Gràcia-Lavedan E, Aragonés N, Pérez-Gómez B, Pollán M, Amiano P, Jiménez-Zabala A, Castaño-Vinyals G, Roca-Barceló A, Ardanaz E, Burgui R, Molina AJ, Fernández-Villa T, Gómez-Acebo I, Dierssen-Sotos T, Moreno V, Fernandez-Tardon G, Peiró R, Kogevinas M, Villanueva CM. Long-term exposure to trihalomethanes in drinking water and breast cancer in the Spanish multicase-control study on cancer (MCC-SPAIN). Environ Int. 2018 Mar;112:227-234. doi: 10.1016/j.envint.2017.12.031. Epub 2017 Dec 28.
- IARC (1991). Monograph on the Evaluation of Carcinogenic Risk to Human: Chlorinated Drinking Water, Chloroform By-product, Some Other Halogenated Compound Cobalt and Cobalt Compound, 52 Lyon IARC, 1991.
- IARC (2013) Monographs on the Evaluation of some chemicals present in industrial and consumer Products food and drinking-water, 101 Lyon IARC, 2013.
- Mohamadshafiee MR, Taghavi L. Health Effects of Trihalomethanes as Chlorinated Disinfection by Products: A Review Article. World Academy of Science, Engineering and Technology International Journal of Environmental and Ecological Engineering Vol:6, No:8, 2012

Co-funded by the Health Programme of the European Union

EU funding disclaimer: This project has received funding from the 3rd European Union Health Programme 201-2020 under Grant Agreement PP-2-5-2016 (# 769767)

4. General conclusion

All scientific articles of population studies (case-control, cohort, etc.) we have researched and analyzed correlate the exposure to the main persistent contaminants (mainly POPs) and the risk of breast cancer; in our evaluation. we either found a statistically significant risk or no risk (denied studies) for breast cancer. To critically review the eligible articles, we evaluated inclusion criteria for participants, appropriateness of controls and reference groups, exposure assessment, whether the range of exposure (from no or low exposure to high) provides a strong comparison, control for confounding, the length of follow-up after exposure to allow for disease latency. We researched and analyzed **11 IARC monographs** on specific contaminants (e.g. PCBs, DDT, dioxins, atrazines, PAHs, PFOA, cadmium, trihalomethanes and its metabolites); we also reviewed **24 scientific reviews**, for a total of **130 scientific study articles** (see table 1), of these, 84 did not reveal a statistically significant risk for breast cancer (NO ASSOCIATION), while 46 scientific articles , found a statistically significant correlation between exposure to the contaminant and breast cancer (POSITIVE), even for a single molecule and/or congener (e.g. PCB).

Tab. 1 – Scientific Articles researched for different persistent pollutant family and breast cancer risk.

Contaminants	number of scientific articles	NO ASSOCIATION scientific articles	POSITIVE scientific articles
PCBs (209 congeners)	38	20	18
DDT, DDD, DDE and principal Organachlorines Compounds	40	33	7
Dioxins (TCDD)	13	8	5
PAHs	14	8	6
PFAA (PFOS, PFOSA and PFOA)	6	3	3
Triazine	8	7	1
Cadmium (Heavy Metal)	6	3	3
Trihalomethanes (THMs)	5	2	3
TOTAL Scientific Articles	130	84	46

Co-funded by the Health Programme of the European Union

EU funding disclaimer: This project has received funding from the 3rd European Union Health Programme 201-2020 under Grant Agreement PP-2-5-2016 (# 769767)

We reviewed much of the literature on environmental pollutants and breast cancer and we found different scientific articles that supported positive associations with different congeners of polychlorinated biphenyls PCBs, DDE and PAHs in combination with certain genetic polymorphisms, and for exposure to cadmium, trialomethanes and dioxins, but most of the case-control studies examined do not find a statistically significant association between the exposure to contaminated persistent and the risk of breast cancer.

The persistent bioaccumulative organochlorines PCBs and DDT, DDD, DDE remained frequently studied, though nearly all studies still relied on biological measurements collected at or after diagnosis, which may capture exposures relevant to cancer promotion (but not earlier stages of breast cancer development). Two cohorts in particular provide unique opportunities to examine relevant periods of exposure. In the Child Health and Development Studies (CHDS), blood samples collected during pregnancy in the 1950-1960 allowed evaluation of breast cancer risks associated with DDT and PCBs exposures in early life, including in utero, during a period of high exposures **[Cohn 2007, 2012, 2015].**

Clearly, the correlation between exposure to environmental contaminants and breast cancer risk may also be associated with other persistent environmental contaminants. From the beginning of the study design, however, we focused on the main classes/families of persistent contaminants that are present in the environmental monitoring plans of the various Environmental Protection Agencies. In line with current European and national legislation in the field of water protection and of the soil these agencies carry out annual and various monitoring environmental campaigns on different environmental matrices (deep water and soil) across the European countries,.

Results are summarized in Annexes 1-8, in the form of tables, for the main classes of persistent contaminants.

Co-funded by the Health Programme of the European Union

EU funding disclaimer: This project has received funding from the 3rd European Union Health Programme 201-2020 under Grant Agreement PP-2-5-2016 (# 769767)