Environmental and industrial toxicology

ASSESSMENT OF EXPOSURE TO PERSISTENT ORGANOCHLORINE COMPOUNDS IN EPIDEMIOLOGICAL STUDIES ON BREAST CANCER: A LITERATURE REVIEW AND PERSPECTIVES FOR THE CECILE STUDY

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Key words: exposure assessment, organochlorine compounds, epidemiologic studies, physiologically-based pharmacokinetic models

ABSTRACT

Breast cancer is the most frequent neoplastic disease in women representing 50,000 new cases each year in France. The well-established risk factors, as those related to the reproductive history, cannot account for all cases of breast cancer. Other environmental or lifestyle factors need to be explored in depth. Persistent organochlorine compounds (OCs) have attracted attention because of their endocrine disrupting properties that make them possible risk factors for breast cancer, but most epidemiological studies did not report an association between OC concentrations in blood or adipose tissue and breast cancer risk. In these studies, OC levels were measured in biological samples obtained at the time of cancer diagnosis or only a few years before.

In this paper, we review the studies on dichlorodiphenyltrichloroethane (DDT) and polychlorobiphenyl (PCB) exposures in relation to breast cancer. We discuss the relevance of OC biological measurements as lifelong exposure indicators, and we describe a new method for assessing exposure to OCs in epidemiological studies.

Most studies were carried out recently and reported OC concentrations that were substantially lower than those reported during the 1960s and 1970s. We make the assumption that these OC levels were not reliable indicators, as they were not measured during etiologically relevant periods in a woman's lifetime, i.e. during the prenatal period, the puberty or the period before a first full-term pregnancy, which are regarded as key periods of vulnerability of mammary gland cells to carcinogens.

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This may have resulted in non differential exposure misclassification and hence in the absence of an observed association between OC levels and breast cancer in most epidemiological studies.

Physiologically-based pharmacokinetic (PBPK) models allow estimating persistent organic pollutant lifetime toxicokinetics profiles retrospectively in women, by taking into account individual differences in metabolism and key events that affect OC kinetics such as lactation and weight variations. PBPK models will be applied to the participants of a large French population-based case-control study including 1080 cases and 1055 controls.

Exposure misclassification could have prevented from observing an association between exposure to OCs and breast cancer risk. PBPK models could be used as a novel way of assessing exposure to OCs and to investigate the impact of internal exposure at different time windows on breast cancer incidence.

BACKGROUND

Breast cancer is the most frequent neoplastic disease in women representing 50,000 new cases each year in France (1). Moreover, the incidence of the disease has increased regularly over the last decades in most countries and the spread of screening programs does not entirely explain that increase (2). The established risk factors, as those related to hormonal and reproductive factors in women (early menarche, parity, late age at first birth, etc.), obesity in menopausal women or hormone replacement therapy, cannot account for all cases of breast cancer (3). Genetic factors which confer an extremely high risk in mutation carriers, particularly the BRCA1 and BRCA2 genes, are involved in only 5% of all breast cancer cases (4). DNA microarrays used to screen the whole human genome have permitted to identify new alleles related to human breast cancer, but these alleles are associated with a weak relative risk and can explain only a small part of the genetic component of breast cancer (5). These data suggest that other factors, particularly environmental or lifestyle factors, as well as gene-environment interactions may also play a role in breast cancer etiology (6).

The role of environmental factors in breast cancer has been a matter of concern in recent years, as many environmental pollutants may contribute to breast cancer risk by damaging DNA or by promoting tumor growth. A recent review has identified 216 potential mammary carcinogens in animals (7). Additionally, in vitro assays have identified approximately 250 chemicals that mimic or interfere with estrogen metabolism, stimulating the growth of mammary gland cells (8). These chemicals could similarly affect human breast tissue.

Organochlorine compounds (OCs) have attracted particular attention because of their environmental impact and their long half-life in biological tissues. The insecticide dichlorodiphenyltrichloroethane (DDT) and the family of polychlorobiphenyls (PCBs) are the chemicals that have been the most frequently studied in relation to breast cancer. Despite the ban of DDT in France and other European countries in the 1980s (9) and the restriction of PCBs use in the same period (10), they bioaccumulated along the food chain and remain ubiquitous in the environment.

DDT was first used worldwide in 1939 as a control vector of malaria. In the 1960s, it was widely used as an insecticide in agriculture in Western countries. Diet, particularly meat, fish and dairy products, represents today the main source of exposure of the population (11). OCs are detectable in adipose tissues, the primary place where they are stored, but can also be detected in blood (12). While DDT has an estimated half-life of about 4 years in human, the half-life of DDE (1,1-dichloro-2,2-bis(4-chlorophenyl)ethene), the principal metabolite of DDT, is much longer, accounting for its greater concentration in humans (13). For this reason, DDE is used as the main biomarker of exposure to DDT in epidemiological studies.

PCBs include 209 congeners. They were first synthesized in the 1930s. They are particularly stable chemicals and were used in a wide range of applications, including dielectric fluids in transformers and capacitors, heat transfer fluids, and lubricants (10). Review of the literature reveals uncertainty in the estimated half-lives of PCBs (14).

OCs have been suspected to play a role in breast cancer. Several epidemiological studies have investigated breast cancer risk in relation to OCs concentrations measured in blood or in adipose tissue. In this article, we review the studies on DDT/DDE and PCBs in relation to breast cancer. We discuss the relevance of using exposure biomarkers as lifelong exposure indicators, and we describe an innovative method for assessing exposure to OCs that we plan to apply for the first time in a large population-based case-control study on breast cancer.

EPIDEMIOLOGICAL STUDIES ON OC AND BREAST CANCER RISK

Epidemiological studies on OC concentrations in biological tissues in relation to breast cancer risk include prospective cohort studies and population- or hospital-based case-control studies. In prospective cohort studies, tissue samples of cohort members are collected at initiation of follow-up in healthy women. At the end of follow-up, OC concentrations of women diagnosed with breast cancer are compared to those of controls selected in the cohort among disease-free women (nested case-control study). OC levels are thus measured in biological samples collected a few years or months before the diagnosis of cancer. In population- or hospital based case-control studies, OCs are measured in biological samples that are contemporary to the date of diagnosis.

Figure 1 presents the findings of the studies published since 1993 separately for nested case-control studies and for population- or hospital based case–control studies. It shows the odds ratios (ORs) of breast cancer and the 95% confidence interval for the highest versus the lowest exposure percentile of DDE and PCB concentrations measured in the blood or in adipose tissue.

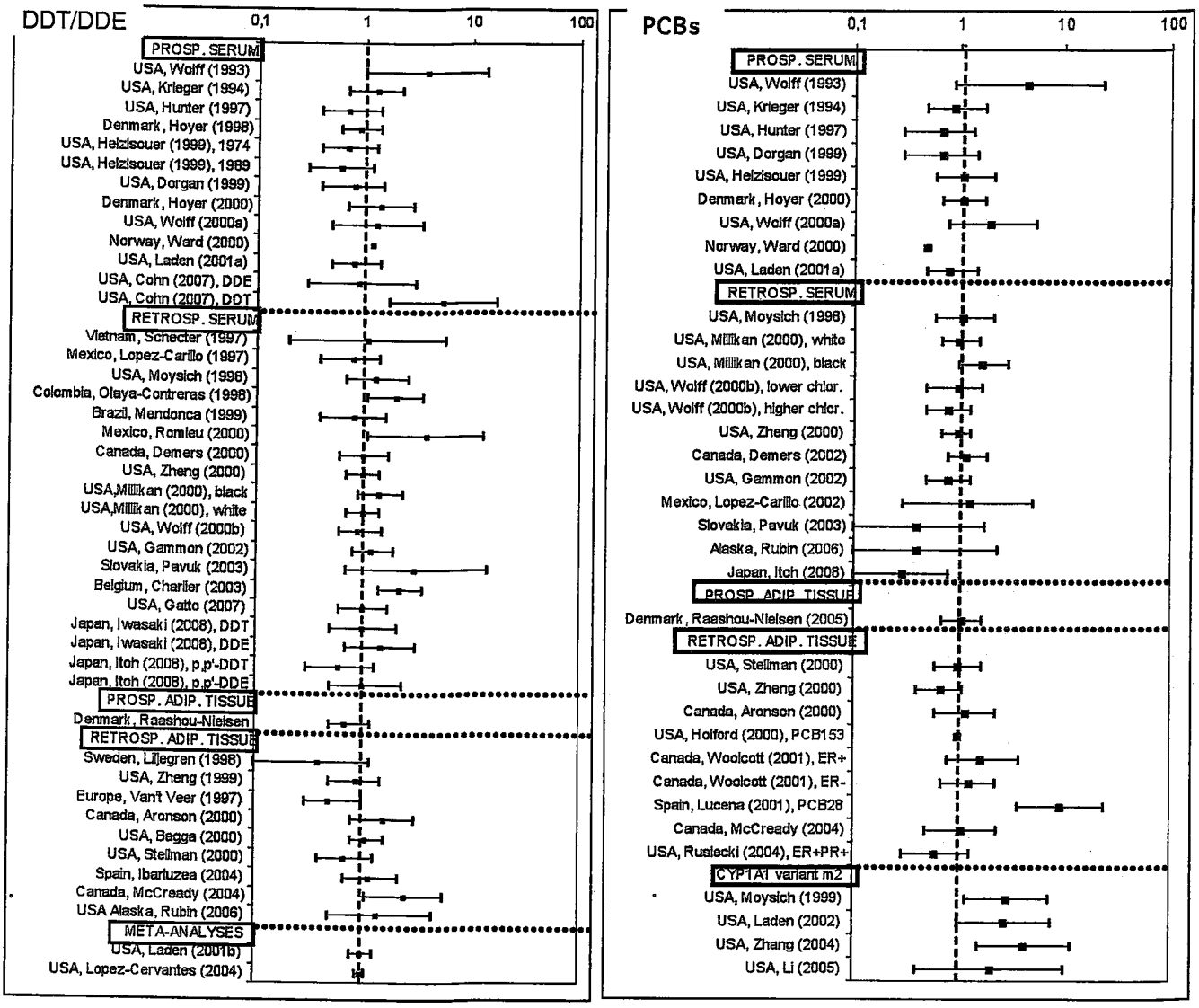

Figure 1: *Studies on breast cancer and DDT or PCBs measurements in serum or adipose tissue. OR with 95% confidence interval for DDE/DDT (left) and PCB (right).*
PROSP. SERUM: prospective cohort study. Measurements made in serum. RETROSP. SERUM: population- or hospital-based case-control study. Measurements made in serum. PROSP. ADIP. TISSUE: cohort study. Measurements made in adipose tissue. RETROSP. ADIP. TISSUE: population- or hospital-based case-control study. Measurements made in adipose tissue. CYP1A1 variant m2: epidemiological study with stratification on according to polymorphism CYP1A1. ORs in the variant m2 strata.

DDT/DDE: In the early 1990s, Wolff et al. (15) conducted a case-control study nested within the cohort of New York University women and reported a 4-fold increased risk of breast cancer for women in the highest DDE exposure quintile as compared to the women in the lowest quintile (OR=3.68 [1.01-13.50]). Other studies reported an association between DDE/DDT and breast cancer (16,17,18,19), particularly in Colombia (18) and Mexico (19) where DDT was still in use at the time of blood collection as a control vector of malaria or dengue. However, most studies conducted subsequently, did not report an association between OC concentrations and breast cancer. No association was seen overall or in strata defined by menopausal status, estrogen or progesterone receptor status, or polymorphisms in genes involved in the metabolism of xenobiotics (20,21,22,23,24,25,26,27,28). Meta-analyses (25,26) confirmed the absence of association with a pooled OR of 0.99 [0.77-1.27] in one study (25) and of 0.97 [0.87-1.09] in another (26).

PCBs: There is currently no evidence of an association between PCBs and breast cancer risk. With a few exceptions where breast cancer was positively (29) or negatively (23) associated with PCBs, studies did not report statistically significant associations of breast cancer with total PCBs, or groups of PCB congeners defined by their chemical activity. Results for individual PCB congeners were inconsistent (30,31). However, four studies (32,33,34,35) reported that PCB levels were associated with breast cancer risk in women carrying a particular polymorphism of the gene encoding the CYP1A1, an enzyme involved in the metabolism of PCBs and other xenobiotics. This possible interaction between PCBs and CYP1A1 is of interest and needs to be replicated in larger studies.

RELEVANCE OF OC MEASUREMENTS IN EPIDEMIOLOGICAL STUDIES

Limitations of OC measurements

The lipid-adjusted levels of DDE in blood reported in epidemiological studies are shown in Figure 2. DDE levels measured in biological media collected since

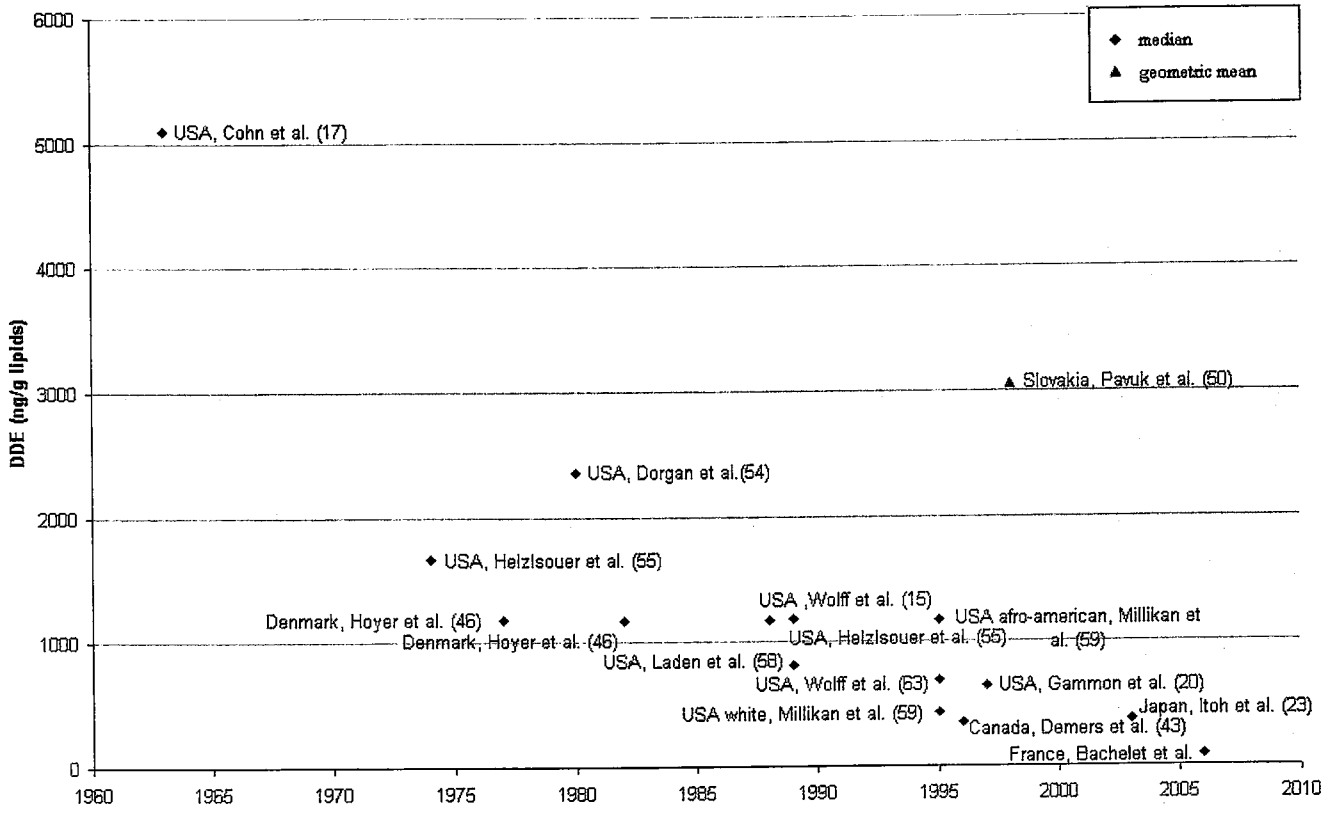

Figure 2: Median DDE concentrations in blood reported in epidemiological studies by mean year of blood draw. Values shown are median or geometric means depending on what was given in the original article.

Only studies that reported lipid-adjusted levels in blood samples were included. Organochlorine levels are not age-adjusted, so some differences by study population could be due to age differences.

the late 1980's are substantially lower than those observed during the 1960s or 1970s. Figure 2 shows that DDE levels were approximately 8 times lower in 1997 (20) than in 1963 (17). These figures demonstrate that current values of OC concentrations cannot be taken as a measure of cumulative exposure over lifetime.

In contrast, epidemiological studies have implicitly assumed that the biological measures of OCs reflect historical lifelong exposures. We believe that this assumption is inadequate, because it has been demonstrated that OC measurements also reflect individual differences in metabolism and key events that affect OC kinetics in the entire lifespan of the women, such as lactation and weight variations (36). In particular the concentrations of OCs observed in recent studies do not simply reflect concentrations earlier in life, but also a potentially large number of events that could affect the current body burden of OCs. As a consequence, the pharmacokinetic variability is a possible cause of non differential exposure misclassification in epidemiological studies, which usually bias the odds ratio toward unity. This limitation may explain that no association of OC measures with breast cancer was observed in the epidemiological studies carried out so far.

Periods of vulnerability

Additionally, measuring OCs in biological sample collected at inclusion in the study do not allow the assessment of internal exposure during critical time windows of a woman's lifetime. Carcinogenesis models highlight the importance of exposure assessment at different critical periods of the mammary gland development where increased susceptibility to carcinogens may occur, such as the perinatal period, the puberty, or the full time-span before the first full-term pregnancy (37). This is exemplified by studies on breast cancer incidence among Japanese atomic bomb survivors exposed to radiations showing that exposure at a lower age has a higher impact on cancer development than exposure at later-life stages (38). A recent study (17) reported that exposure to DDT early in life may increase the risk of breast cancer. High levels of serum DDT were associated with a statistically significant 5-fold increased risk of breast cancer among women who were born after 1931. These women were under 14 years of age in 1945, when DDT came into widespread use, and mostly under 20 years when DDT use peaked.

A NEW APPROACH

Physiologically-based pharmacokinetic modeling of OCs

Verner et al., 2008 (39) developed a physiologically-based pharmacokinetic (PBPK) model that allows characterizing retrospectively the lifetime toxicokinetic profile of internal exposure to persistent organic pollutants. This model permits to characterize OC flow between nine compartments of the human body which represent organs (i.e., adipose tissue, liver, brain, mammary tissue, uterus, placenta, foetus) or lumps of organs (i.e., richly and poorly perfused tissues), as well as excretion through metabolism and lactation. The kinetics of OC is described using mass balance differential equations that integrate information on organ/blood lipid content, organ volume, blood flow to organ, and the log octanol:water (Kow) partition coefficient. Metabolism is assumed to be limited to the liver compartment and defined as an intrinsic clearance calculated with half-life values found in the literature. Loss via lactation is modeled as an extraction from the mammary tissue following breast milk excretion and blood:milk partition coefficient. The dose is set as a direct input in the liver compartment as OCs are assumed to be fully absorbed from the intestinal tract and to undergo first-pass metabolism. Oral dose can be either estimated from information gathered in questionnaires or by an optimization process to match a sampled blood level. The model integrates individualized information on subjects' physiologic profile (i.e., body weight and height as a function of age) and history (i.e., age at pregnancies and duration of breast-feeding periods) to evaluate organ/blood OC levels for any hypothesized period of susceptibility.

Although this model was not validated for women on a period spanning several years, they recently validated the mother-infant transfer of OC through breast milk, a major route of excretion that impacts OC toxicokinetics in women (40).

The CECILE case-control study

The CECILE study is a population-based case-control study that aimed at investigating environmental risk factors of breast cancer. It was conducted in well-defined geographic areas in France (*départements* of Ille-et-Vilaine and Côte d'Or). The cases were women residing in these areas and were diagnosed with invasive or in situ breast cancer during the study period (2005-2007). Histologically confirmed cancer cases

aged between 25 and 75 years at diagnosis were included.

The controls were randomly selected among women of the same age as the cases residing in the same areas, and who never had a breast cancer at the time of inclusion in the study. They were recruited by telephone using a random digit dialing method. If the household included a woman meeting the inclusion criteria, she was invited to take part in the study within the limit of quotas by age and socioeconomic status (SES). To avoid selection bias, the distribution by SES of the control group had to reflect the SES distribution of the study area as a whole, as documented by the population census. After selection, controls were contacted rapidly for an in-person interview and blood draw.

The cases and the controls were interviewed by nurses using a structured questionnaire. Detailed information on hormonal and reproductive factors (age at menarche, reproductive history, menopausal status, contraceptive use, etc.), anthropometric data, personal medical history, family history of cancer, hobbies, residential history, detailed occupational activities and dietary habits were obtained. A blood sample was requested at the end of the interview, and 2135 women (1080 cases and 1055 controls) accepted to give blood. Plasma concentrations of pesticide residues (p,p'-DDT, p,p'-DDE) and PCBs (PCB congeners 28, 52, 101, 118, 153, 138, 180) were measured in these blood samples. The analyses included a measure of total cholesterol and triglycerides in order to standardize OC levels on total lipids. The measurements were carried out in the toxicology laboratory of the Sart-Tilman University Hospital in Liège, Belgium.

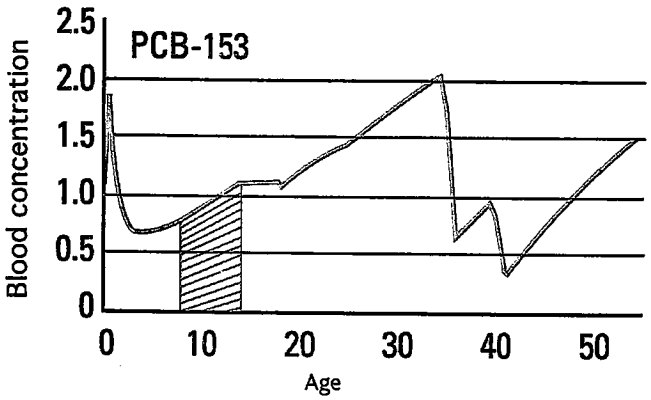

Figure 3: *Example of a toxicocinetic profile obtained from the PBPK models.*

This subject is 55 years old at the time of blood draw. She was breast-fed for 6 months in childhood, was exposed to 18.7 ng/kg/day PCB-153, and had two pregnancies at 35 and 40 years of age followed by 12-month lactation periods.

Applying the PBPK models in the CECILE study

The lifelong exposure profile of each participant in the CECILE study is being assessed retrospectively for PCB 153 using the values of PCB 153 measured at the time of sampling. In a first step, PCB 153 is used as it is highly correlated to other PCB congeners.

Information collected in the questionnaire, such as body weight at every decade of life, height, age at deliveries and breastfeeding periods, are integrated in the PBPK modeling to extrapolate individualized physiologic profiles. Information on food contamination by PCBs during different calendar periods was collected from environmental databases and from the scientific literature, and is also integrated in the models.

The uncertainty regarding biological parameters in the PBPK models, as lipid and water fractions, intrinsic clearance, fraction of lipids in breast milk, is taken into account using Monte Carlo analyses. An example of toxicokinetic profile is shown in Figure 3. Areas under the curve (AUC) for different periods will be used as exposure proxy for the PCBs.

Associations between internal exposure and incidence of breast cancer will be tested with hierarchical models of regression using a Bayesian approach to take into account the variability obtained with the Monte Carlo simulations. As an example, Figure 3 shows the AUC for the period between the age of 8 and the age of 14 (AUC8-14). AUC8-14 will be used as an indicator of internal exposure during puberty, a critical exposure window in breast cancer etiology.

CONCLUSION

There is a biological plausibility that OCs play a role in breast cancer etiology. However, most epidemiological studies reported no association between OC levels in blood or adipose tissues and breast cancer risk.

Exposure misclassification could have prevented from observing an association between exposure to OCs and breast cancer. We suggest that exposure as-

sessment could be improved by using PBPK models in epidemiological studies.

These PBPK models can be used as a novel way for assessing exposure to OC and investigating the impact of internal exposure during different time windows on the incidence of breast cancer. In this approach, exposure misclassification could be minimized. PBPK models should also allow the study of OC exposure during critical time windows connected to the periods of vulnerability of mammary gland cells to carcinogens.

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