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# Pollutants make rheumatic diseases worse: Facts on polychlorinated biphenyls (PCBs) exposure and rheumatic diseases

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ABSTRACT

*Background:* Polychlorinated biphenyls (PCBs) are persistent organic pollutants that bioaccumulate in adipose tissue, disturbing its metabolism and the balance of adipokines, related to obesity. The altering secretion pattern of adipokines from the adipose tissue and the increasing mechanical load in weight-bearing joints presented in obesity condition, are risk factors for osteoarthritis development. The most prevalent rheumatic diseases, osteoarthritis and rheumatoid arthritis, are chronic conditions that target the whole joints, leading to increasing disability and health care cost. The goal of this focused review is to summarize the current knowledge on the role of PCBs in osteoarthritis and rheumatoid arthritis pathogenesis.
*Search strategy:* A PubMed search was managed using keywords as "rheumatic diseases", "polychlorinated biphenyls", "obesity" and "endocrine disruption".
*Main results of the review:* The incidence of rheumatoid arthritis has been reported to be increased especially in urban areas in industrialized countries, emphasizing the importance of environment in the pathogenesis of rheumatic diseases. Analysis of two cohorts exposed to PCBs food contamination showed high incidence of arthritis. In addition, PCBs in serum correlated positively with the prevalence of self-reported arthritis. Few studies support the hypothesis that osteoarthritis development could be related to PCBs induction of chondrocytes apoptosis.
*Conclusion:* Evidences have emerged for a relationship between PCBs and development of several types of arthritis. Further research is encouraged to determine the correlation between PCBs exposure and the development of rheumatic diseases.



## 1. Introduction

Rheumatic diseases represent a multitude of degenerative, inflammatory and auto-immune conditions that targets the joints, affecting a significant portion of the population and leading to increasing disability and health care costs. The most prevalent rheumatic diseases are osteoarthritis (OA) and rheumatoid arthritis (RA) [1]. (See Table 1.)

OA is a disease that affects the whole joint, with an irregular cartilage structure characterized by a reduction in the number of chondrocytes, loss of extracellular matrix, synovial inflammation and remodeling of subchondral bone with formation of osteophytes [2,3]. On the other side, RA is a chronic, systemic autoimmune disease characterized by inflammation and hyperplasia of the synovium, which is the result of an imbalance between proliferation and apoptosis of resident cells, including fibroblast-like synoviocytes. RA also results in destruction of cartilage and bone [4]. Unlike in RA, osteoarthritic cartilage contains a higher percentage of chondrocytes undergoing apoptosis than normal cartilage. This is believed to be due to the increased production of nitric oxide (NO) by OA chondrocytes as a consequence of the up-regulation of NO synthase (NOS) induced by pro-inflammatory factors [5,6].

While the underlying mechanisms in pathogenesis of OA and RA are not fully understood, it is generally accepted that the interplay between genetic predisposition and environmental factors contributes to the development of these two common types of arthritis [7]. For instance, the increasing prevalence of OA in the United States is likely attributable, at least in part, to the increasing aging population and obesity [8]. Excess of body weight may lead to cartilage degeneration by increasing the mechanical forces across weight bearing joints. Nevertheless, metabolic factors produced by white adipose tissue (WAT), may also be responsible for the high prevalence of OA among overweight and obese people [9]. Adipocyte-derived molecules, better known as "adipokines", are

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**Table 1**
Summary of findings of cohort studies.

| Country | Type of study | Participants | Assessment | Result | Ref. |
|---|---|---|---|---|---|
| Japan | Retrospective (from 2001 to 2004) | 501 from Yusho cohort | PCB blood concentration<br>Medical/laboratory examination | Positive correlation between PCB serum levels and arthralgia | [46] |
| Taiwan | Follow-up (14 years) | 795 from Yucheng cohort | Phone interview | High prevalence of reported arthritis in Yucheng men | [48] |
| USA | Cross-sectional | 1721 from NHANES (1999–2002) | PCB blood concentration<br>Self-reported arthritis | Positive association between PCB serum levels and self-reported arthritis, mainly rheumatoid arthritis, in women | [49] |

likely to be important mediators linking obesity and adiposity with inflammation and OA [10]. Since the world-wide incidence of RA has markedly increased in recent years, especially in urban areas, it is plausible that this increase in the prevalence of RA could be attributed, at least partly, to increased exposure to various environmental factors.

The present paper reviews recent lines of evidence of the role played by environmental pollutants PCBs in the development of rheumatic diseases, especially OA and RA.

## 2. Search strategy

Papers discussed in this Review were identified from MEDLINE database with searches on PubMed and online journals. Only peer-reviewed, English-language journals were included in the search. Papers published after 2006 were preferentially selected, but relevant papers published earlier were also included [11]. The following search terms were used in various combinations: “rheumatic diseases”, “osteoarthritis”, “rheumatoid arthritis”, “matrix degradation”, “systemic lupus erythematosus”, “chondrocytes”, “environmental pollutants”, “polychlorinated biphenyls”, “obesity”, and “endocrine disruption”.

## 3. Polychlorinated biphenyls (PCBs)

Polychlorinated biphenyls (PCBs) are aromatic, synthetic chemicals which do not occur naturally in the environment. They consist of the biphenyl structure with two linked benzene rings in which some or all of the hydrogen atoms have been substituted by chlorine atoms (Fig. 1). They have been employed in the industry on a large scale during the first half of the last century as dielectric and coolant fluids, i.e., in capacitors, transformers and electric motors. Due to their toxicity and persistency in the environment, PCBs production was forbidden by USA in 1979 and by the Stockholm Convention on Persistent Organic Pollutants (POPs) in 2001. Despite the adoption of restrictive rules, to date, certain levels of PCBs are still detected in outdoor air, seawater and sediments of waterways, although concentrations had dropped to one quarter or less of their levels in the late 70s [12].

These pollutants, due to their high chemical stability and lipophilicity, tend to bioaccumulate mainly in lipid-rich tissues, as well as to biomagnify in the food chain (Fig. 2) [13]. Ingested sources account for the bulk of human exposure. Occupational exposure affects only a limited slice of the population, but accidental exposure rarely occurs. Indeed the daily human exposure is, in 90% of cases, due to contaminated foods (90% of animal origin, especially fish and dairy products) [14]. An estimate of adult human PCB exposure is 2–6 ng/kg/day via food [15]. However, lighter congeners can also be volatile and inhaled. The improper efficiency for the incineration of municipal solid waste (MSW), such as incomplete combustion of the waste,

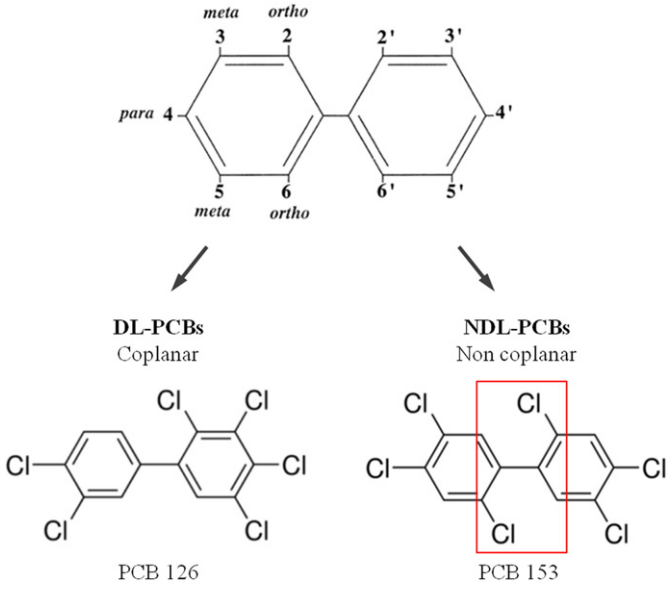


**Fig. 1.** Chemical structure of PCBs. The common structure of PCBs consists of biphenyl structure with chlorine substitution. Dioxin like-PCBs (DL-PCBs) do not present *ortho*-chlorine and adopt a coplanar structure. Non-dioxin like-PCBs (NDL-PCBs) present, at least, two chlorine substitutions on *ortho*- positions (red square), and they have non-coplanar structure.

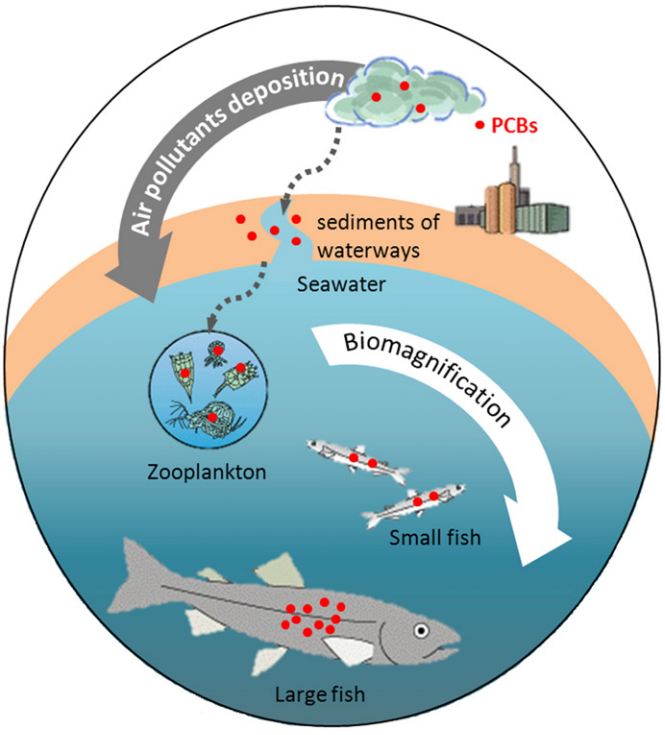


**Fig. 2.** Biomagnification of PCBs. PCBs are released from multiple sources. Due to their lipophilicity, these chemicals tend to bioaccumulate in lipid-rich tissues and to biomagnify in the food chain.

represents also a well-known source of PCBs. In order to give a magnitude of this aspect, in the United States there are 167 MSW incineration units with larger than 250 tons per day incineration capacity, that may contribute significantly to PCBs emission [16,17].

PCBs are a group of 209 congeners with a broad spectrum of biological and toxic effects. PCB congeners can be divided into two major groups, namely dioxin-like (DL-) and non-dioxin-like (NDL-) PCBs. Mixtures of PCBs are generally evaluated on the basis of chemical analysis where the properties of six PCBs, which are often referred to as "indicator" PCBs (iPCBs; IUPAC nos. 28, 52, 101, 138, 153 and 180). These compounds are considered to be markers of pollution caused by all PCBs. The sum of five iPCBs (excluded the PCB 118 which is a dioxin-like congener, DL) accounts for the 50% of total non-dioxin like (NDL) congeners in food [12]. Although NDL-PCBs are less toxic than DL congeners, these pollutants are equally harmful since they have been detected at much higher concentration levels than the latter congeners, in blood and tissues of humans, wildlife and fish exposed via the food chain to environmental PCBs [18].

Chemical properties and toxic effects of PCBs are strictly structure-dependent. Their lipophilic character and their capability to persistence in the environment are directly related to the degree of chlorination. Moreover, toxic effects of PCBs depend on the positions of chlorine atoms and consequently on the steric structure of the molecule.

The Aryl hydrocarbon receptor (AhR) is a ligand-dependent transcription factor that mediates toxicological effects that result from exposure to halogenated aromatic hydrocarbons such as PCBs [19]. Those PCBs that do not present *ortho* chlorines adopt a coplanar structure similar to dioxins (DL-PCBs) and, as a consequence, they have high-affinity binding to the AhR (Fig. 1) [20].

On the other hand, NDL-PCBs have at least two chlorine substitutions at the *ortho*-positions on the biphenyl ring that twists the structure away from a single plane. This non-coplanar structure reduces the affinity for AhR (Fig. 1). Indeed these compounds are likely to act as inhibitors of AhR-mediated activation [21]. It is becoming increasingly clear that NDL-PCBs are more likely to act as ligands for members of nuclear receptor family of transcription factors [22]. It has been suggested that these congeners may act as ligands for constitutive andostane receptor (CAR) and/or pregnane X receptor (PXR), and may thus activate CAR/PXR target genes expression, that encode three phases of xenobiotic metabolizing enzymes [23,24].

Although most of PCBs do not show an acute toxicity, their chemical inertness, remarkable stability and lipophilicity, which determine their tendency to bioaccumulate in lipid-rich tissue, make them mainly responsible for chronic toxic effects. A growing body of evidences have demonstrated that PCBs are mainly involved in alterations of signal transduction systems, neurotoxicity, immune suppression and endocrine disruption [25,26].

## 4. PCBs as endocrine disruptors

The term "endocrine disrupter (ED)" was first used at the Wingspread Conference in 1991, and referred to those endocrine active substances which may alter endocrine system and homeostasis [27].

PCBs are, therefore, POPs that accumulate preferentially in adipose tissue (AT), which it is actually recognized as an endrocrine organe due to its ability to secrete adipokines [28]. Recently, various interactions between AT and POPs have been reported, suggesting that this tissue plays a significant role in the toxicity of POPs [29,30]. As reviewed by La Merrill and co-workers, AT has three basic toxicological implications: it acts as a reservoir for POPs; it constitutes a low-grade internal source of stored POPs leading to continuous exposure of other tissues; and it can be a target for the POPs which can affect AT functions, increasing its inflammatory state, and/or modulating the differentiation of adipocyte precursor [31]. As a consequence, by targeting this tissue, PCBs can exert an obesogenic effect.

The prevalence of obesity was increased dramatically over the last three decades in all over the world [32]. Increasing evidence suggests that the commonly held causes of obesity, which are over-eating, inactivity and genetic pre-disposition, do not fully explain the current obesity epidemic. Interestingly, the production and use of synthetic chemicals have increased dramatically, in parallel with growing obesity. This has led to consider the influence of other factors and it has been suggested that endocrine disruptors may play a key role in obesity development by altering metabolic control mechanisms [33]. This hypothesis is supported by several in vitro and in vivo studies, as well as epidemiological evidence, demonstrating that some endocrine disruptors (e.g. PCBs) may affect adiposity and obesity incidence [34–37]. Therefore PCBs could increase the proliferative capacity of fat cell precursors, probably promoting a fat mass gain.

Obesity is also characterized by a chronic low-grade inflammation status, macrophage accumulation in fat tissues and dysregulated adipokines synthesis and secretion [38]. Several studies have shown that PCBs, mostly the NDL-congeners, may upregulate levels of the adipokine leptin, probably leading to final obesogenic effect [39,40]. Two years ago, Ferrante and co-workers demonstrated that NDL-PCBs 101, 153 and 180 are able to induce disruption of lipid metabolism through the reduction of leptin receptor responsiveness and its related pathways. In addition, the authors showed that these PCBs are able to significantly induce two pro-inflammatory cytokines, IL-6 and TNF-α [41].

## 5. PCBs exposure and development of rheumatic diseases: facts and figures

Obesity is also a risk factor of paramount relevance for OA. In addition to negative effects of increased body mass on weight-bearing joints, altered metabolic changes due to adipose tissue dysfunction have recently been proposed as one of the underlying mechanisms of OA [42,43]. In particular, we and other groups have demonstrated that leptin might participate in damage that occurs in joints by altering the production of pro-inflammatory and pro-catabolic factors involved in the onset and/or progression of OA [44–46]. Noteworthy, PCBs, mostly NDL-congeners, may upregulate leptin levels. Thus, taking into account that OA pathogenesis is associated with adipokines and NDL-PCBs alter adipokines expression, it is plausible to speculate that these pollutants could be involved in the pathogenesis and/or progression of OA.

However, only few studies have analyzed the correlation between exposure to PCBs and the development of OA.

In 1968, an unprecedented mass food poisoning occurred in the west of Japan. It was called "Yusho" incident (yusho means oil disease in Japanese). Approximately 1900 individuals were accidentally exposed to high levels of PCBs through the ingestion of rice oil contaminated with Kanechlor-400, a Japanese commercial brand of PCBs. Serum concentrations of PCBs in the "Yusho" group correlated with incidence of swelling of the joints and arthralgia [47,48]. After the "Yusho" incident, in 1979, a similar mass food poisoning event caused by the ingestion of cooking oil accidental contaminated with PCBs and dioxins, "Yucheng" (oil disease in Chinese), occurred in central Taiwan. In the cohort of subjects "Yucheng" there was an incidence of arthritis four times higher than the observed in subjects not exposed [49].

A positive correlation between PCBs serum levels and the prevalence of self-reported arthritis in women has been reported in a sample of 1721 adults from the National Health and Nutrition Examination Survey (NHANES) 1999–2002 [50].

Destruction of the cartilage matrix by a pathological imbalance of normal chondrocyte function is a key element in OA progression. Chondrocytes, as the only resident cells in the articular cartilage, preserve the integrity of the cartilage itself. Thus, cell death of chondrocytes was suggested to be responsible for cartilage damage [5,51]. Since PCBs have been associated with the incidence of OA [50], and with the induction of apoptosis in different cell lines [52–55], it has been hypothesized

that PCBs could induce apoptosis also in chondrocytes. In fact, a recent study demonstrated the activity of PCBs on chondrocytes viability through regulation of apoptosis, necrosis and oxidative stress. Three of the PCBs indicators, PCB 101, PCB 153 and PCB 180 were found to induce cell death through necrosis and apoptosis and oxidative stress by decreasing antioxidant capacity [56].

Endocrine disruptors, such as PCBs, markedly influence the immune system [57], increasing the risk of autoimmune diseases, such as RA. However, only the study of Lee and co-workers showed that PCBs were positively associated with RA, and RA was more strongly associated with PCBs than was OA, suggesting that exposure to PCBs may be involved in pathogenesis of RA [50]. In a recent morbidity study evaluating the health status of male steel workers exposed to foundry dust containing also PCBs and dioxins, a significant incidence of RA has been found [58]. From another approach of Di Giuseppe et al., they investigated the association between fish consumption and risk of developing RA, since this is the main source of PCBs exposure for humans. Their results showed a weak inverse association between total fish consumption and risk of RA. The protective effect of long-chain n-3 polyunsaturated fatty acids (PUFAs) presented in fish could explain the lack of statistically significant observed, because of anti-inflammatory properties of these fatty acids [59]. Moreover, the presence of PCBs is lower in cooked fish [60].

Antibodies that target normal self proteins within the nucleus of the cells are called antinuclear antibodies (ANA) [61]. The presence of large amount of ANA can indicate the occurrence of rheumatic diseases such as systemic lupus erythematosus (SLE), Sjögren's syndrome and juvenile arthritis. To this regard, Cebecauer and collaborators reported increased prevalence of ANA in the population exposed to high levels of PCBs [62]. Moreover, a follow-up study in Yucheng people found that SLE in females was highly increased in the later period after PCBs exposure [63].

## 6. Conclusions

Evidences have emerged for a potential involvement of PCBs in the development of rheumatic diseases. Most of the present published results suggest a potential relationship between PCBs and development of several types of arthritis. However, most of them are cross-sectional studies. Thus, to confirm this association, further studies are granted by analyzing patient cohorts prospectively and retrospectively.

## Conflicts of interest statement

The authors declare that there is no conflict of interests regarding the publication of this paper.

## Authors' contribution

OG and VA participated in concept and design of the study, in analysis and interpretation of data, drafting and critical revision of the manuscript, and scientific supervision of the review. TM, MS, JC, CP, JP, FL, MAGG, AM and RG participated in the acquisition, bibliographic research, interpretation of the data, drafting and revising critically the work. All authors approved the final version of the manuscript and agree to be accountable for all aspects of the work.

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