Are Persistent Organic Pollutants Linked to Lipid Abnormalities, Atherosclerosis and Cardiovascular Disease? a Review

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INTRODUCTION

More than 25,000 man-made chemicals have been registered. The term persistent organic pollutants (POPs) is used to denote chemicals with known or suspected adverse health effects in animals or humans and with chemical properties that make them accumulate in the environment, including animals or humans. Lipid-soluble POPs, like dioxins, polychlorinated biphenyls (PCBs) and organochlorine pesticides are transported by lipoproteins and accumulate in adipose tissue. High levels of these compounds in the circulation have been associated with elevated cholesterol and triglycerides in cross-sectional studies and with an increase in mainly low-density lipoprotein cholesterol in a longitudinal study. Also, non-lipid-soluble POPs, such as perfluoroalkyl substances (PFASs) compounds have been associated with increased total cholesterol levels. Carotid artery atherosclerosis has been related to elevated levels of mainly highly chlorinated PCBs and to highly fluorinated PFASs, but in this case only in women. Both cross-sectional and prospective studies have shown dioxins, PCBs, as well as PFASs to be linked to cardiovascular disease (CVD) and mortality. In conclusion, as highlighted in this review, several lines of evidence support the view that POPs of different chemical classes could be linked to lipid abnormalities, carotid atherosclerosis and overt CVD like myocardial infarction and stroke.

Keywords: Toxicology; Lipids; Cardiovascular diseases; Atherosclerosis; Fatty liver
also transported long distances by water and air without breakdown. For example, high levels of the pesticide 1,1,1-trichloro-2,2-bis (4-chlorophenyl) ethane (DDT) have been found in polar bears at Greenland, an arctic island certainly not associated with pesticide use.

POPs could roughly be divided into lipid-soluble and non-lipid-soluble ones. Examples of lipid-soluble POPs are polychlorinated dibenzo-p-dioxins, polychlorinated dibenzofurans, and polychlorinated biphenyls (PCBs), brominated flame retardants and several pesticides, such as DDT. Examples of non-lipid-soluble POPs are the perfluoroalkyl substances (PFASs). A common feature of all these POPs is that they contain a backbone of some of the halogens: Cl, Br, or F. An overview of these POPs is given in Table 1.

PCB production was banned by the United States Congress in 1979, and these soluble POPs, along with some organochlorine (OC) pesticides, were banned in many other countries. In 2001, twelve POPs with known and suspected adverse environmental and health effects were put on a list for limiting the manufacturing and use, the Stockholm Convention (http://www.pops.int), and a majority of the countries worldwide agreed to this convention. In the 2000s, the production of some of the PFASs, like perfluorooctane sulfonate (PFOS) and perfluorooctanoic acid (PFOA), were stopped, but the production of many other forms of PFASs is still ongoing. Despite these bans, since the POPs have been accumulating in the environment for decades, we are still exposed to them, mainly by ingestion of particularly fat fish and meat, and, for the PFASs, also via contaminated water. Furthermore, since these POPs all have a long half-life in humans, levels of PCBs, \( p,p' \)-dichlorodiphenyl-dichloroethylene \( (p,p'\text{-DDE}) \), an active metabolite of DDT, PFOS, and PFOA are still measurable in blood in the majority of subjects living in industrialized countries. The half-lives range from some years to a couple of decades.

**LIPID-SOLUBLE POPS AND CIRCULATING LIPOPROTEINS**

Lipid-soluble POPs, such as PCBs, dioxins, furans, brominated flame retardants and several pesticides are transported to adipose tissue for storage by lipoproteins. For highly lipid-soluble POPs, as much as 99% of the body content of those compounds could be found in adipose tissue, but during conditions without any change in body weight or change in exposure, an equilibrium is met between the circulation and the adipose tissue, so circulating levels could be taken as a good measure of the body burden of lipid-soluble POPs.

Of the lipoprotein particles, low-density lipoprotein (LDL) was found to be the main transporter of lipid-soluble POPs, but very-LDL (VLDL) and high-density lipoprotein (HDL) were also associated with lipid-soluble POPs in humans. It was found that the highly

<table>
<thead>
<tr>
<th>Chemical group</th>
<th>Example(s)</th>
<th>Use</th>
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<tbody>
<tr>
<td>Dioxins-polychlorinated dibenzo-p-dioxins and dibenzofurans</td>
<td>2,3,7,8-tetrachloro-dibenzo-p-dioxin (TCDD)</td>
<td>Dioxins are formed as by-products of numerous types of industrial activity and combustion processes</td>
</tr>
<tr>
<td>PCBs</td>
<td>209 different forms, like PCB126</td>
<td>PCBs were used as coolants and lubricants in transformers and hydraulic oils</td>
</tr>
<tr>
<td>Polybrominated diphenyl ethers</td>
<td>Many different forms, like BDE47</td>
<td>Mainly used as flame-retardant agents</td>
</tr>
<tr>
<td>Organochlorine pesticides</td>
<td>1,1,1-trichloro-2,2-bis (4-chlorophenyl) ethane (DDT)</td>
<td>Fighting malaria</td>
</tr>
<tr>
<td>Perfluoroalkyl substances</td>
<td>Perfluorooctane sulfonate (PFOS)</td>
<td>Water repellent</td>
</tr>
<tr>
<td></td>
<td>Perfluorooctanoic acid (PFOA)</td>
<td>Firefighting foam</td>
</tr>
</tbody>
</table>

PCB, polychlorinated biphenyl; BDE47, polybrominated diphenyl ether-47.
chlorinated PCBs, being the most lipid-soluble PCBs, were more likely to be associated with lipoproteins compared to less chlorinated PCBs. In a follow-up study in the same sample, highly chlorinated PCBs were mainly related to HDL and to changes in several proteins linked to HDL function, such as cholesteryl ester transfer protein and phospholipid transfer protein.\(^8\)

In the Anniston cohort it was noted that the sum of OC pesticides was more closely related to elevations in serum lipids than was the sum of PCBs.\(^9\) In another cross-sectional study, PCB levels were linked to cholesterol and triglyceride levels,\(^10\) and in a Native American sample of Akwesasne Mohawks, serum lipids were mainly related to highly chlorinated PCBs and OC pesticides.\(^11\) In a cross-sectional study from Iran, PCB levels were linked to LDL cholesterol and triglycerides.\(^12\)

In studies in which workers have been occupationally exposed to PCB, serum triglycerides, but not other lipid classes, were found to be increased.\(^13\) In another study including workers exposed to the potent dioxin tetrachlorodibenzo-dioxin (TCDD), both serum triglycerides and serum cholesterol were found to be elevated.\(^14\) In the late sixties and in the late seventies, two populations in Asia were exposed to PCB-contaminated rice bran oil for cooking, the Yushu sample in Japan and the Yucheng sample in Taiwan. In a cross-sectional evaluation of the Yushu population the circulating levels of both cholesterol and triglycerides were found to be elevated.\(^15\) In a cross-sectional study using metabolomics analysis, it was seen that elevated levels of OC pesticides were linked to altered levels of fatty acids, glycerophospholipids, sphingolipids, and glycerolipids, possibly indicating actions also on other lipid classes than those normally measured in the clinic.\(^16\)

The prospective study of the vasculature in Uppsala seniors (PIVUS) study is a population-based cohort of inhabitants in the city of Uppsala, Sweden. The around 1,000 individuals included in the cohort were all aged 70 years and half of the cohort consist of women. The cohort was been reinvestigated also at age 75 and age 80 years. The data collected were initially chosen from a cardio-metabolic perspective, but we have also been able to measure a great number of environmental contaminants in serum/plasma in this cohort.

Since the POPs are transported in lipoproteins, cross-sectional studies are hard to use to interpret regarding the relationships between POP levels and lipid levels. We therefore used data from the PIVUS cohort to evaluate the relationship between POPs and lipids using a longitudinal design. More than 600 subjects free from lipid-lowering agents with lipid and POP levels measured at baseline and lipids remeasured after 5 years. High levels of highly chlorinated PCBs and OC pesticides at baseline were related to an increase in mainly total and LDL cholesterol. The POPs were not related to the change in serum triglyceride levels over the 5-year period. These findings were seen whether or not the levels of POPs at baseline were normalized for total lipid levels at baseline.\(^17\) Thus, these data, together with animal studies showing that POP exposure changed lipid levels,\(^18\) support the view that at least some of the lipid-soluble POPs could alter lipid levels.

It is very common in epidemiological research of health effects of POPs to normalize the POP levels for total lipids in the circulation, since it is assumed that this would more properly reflect the total body POP burden.\(^19\) Usually the sum of triglycerides and cholesterol is used as a proxy for measurements of total lipids. However, given the fact that POPs could change lipids levels, and that the changes in POP levels over 5 years were related to the changes in total lipid levels,\(^20\) it is not clear that lipid-soluble POPs should be normalized for lipids. This
LIPID-SOLUBLE POPS AND LIVER FAT

The role of ectopic fat accumulation and especially lipid accumulation in the liver has emerged as an important risk factor for cardiometabolic diseases in the recent years.

Lipid-soluble POPs have been shown in a number of experimental studies to alter lipid handling in the liver, something that could affect both the lipid levels within the liver, as well as circulating lipoproteins.

Experimental studies have shown that exposure to lipid-soluble POPs could induce fat content in the liver, mimicking non-alcoholic fatty liver disease (NAFLD) in humans.

In one study, mice with high lipid levels were exposed to PCB77 and showed increased liver neutral lipids and decreased serum fatty acid levels. Furthermore, increased messenger RNA (mRNA) expression of genes involved in inflammation, apoptosis, and oxidative stress was seen.21 Also in another study in mice on a high fat diet, PCB153 induced liver steatosis and was associated with reduced expression of hepatic genes implicated in β-oxidation (peroxisome proliferator-activated receptor [PPAR]-α and CPT1A/2) while increasing the expression of genes associated with lipid biosynthesis (fatty acid synthase [FAS]).22

Low-dose exposure of PCBs induced fat accumulation in the liver in zebrafish, being more pronounced in males than females.23 Lipid droplet accumulation in hepatocytes was seen following PCB exposure and the hepatic triglyceride content was significantly increased in both the male and female fish. The expression of mRNA for diacylglycerol O-acyltransferase (DGAT) 1A, PPAR-γ, FAS, and sterol regulatory element-binding protein (SREBP), was upregulated, suggesting increased lipid synthesis.

In hepatocytes in vitro, exposure of the cells to the PCB 126 increased triglyceride levels by altering elimination mechanisms, such as VLDL synthesis and secretion microsomal by alterations in triglyceride transfer protein, SREBP1c and DGAT2.24 In another similar study conducted in human hepatocytes exposed to PCB156, both cholesterol and triglycerides increased.25 Furthermore, more than 200 mRNAs and more than 600 long non-coding RNAs were differentially expressed in the hepatic cells following exposure to PCB156. Amongst the upregulated mRNAs many pathways were found to be related to metabolism, such as estrogen metabolism, omega-hydroxylase P450, epoxygenase P450 and genes being related to insulin receptor signaling. Also, an upregulation of mRNAs being linked to inflammatory processes, such NF-κB, was noted.

Amongst the mRNAs that were downregulated were sphingolipid biosynthesis, apoptotic signaling, as well as immature T cell proliferation in thymus, and cGMP-mediated signaling.

These key enzymes, together with PPAR-α, were found to be changed by a single exposure to PCB126 in rats in vivo. A single PCB126 injection increased hepatic triglycerides concentrations after 1 week.26 Several mRNAs related to lipid metabolism were increased in
the liver, such as fatty acid-binding protein 1 the lipogenic transcription factor SREBP1c and the lipid oxidation transcription factor PPAR-α.

The mechanistic findings regarding PCB effects on lipid handling in the liver in the experimental studies are summarized in Table 2.

Very few studies on POPs and liver steatosis in humans are found. Amongst those, it is worth noting that the age-related accumulation of lipid-soluble POPs in adipose tissue was not seen in the liver.27 One study using the US National Health and Nutrition Examination Survey (NHANES) database found that POP levels were related to an elevation in serum alanine aminotransferase (ALT) activity, which in this study was taken as proxy for NAFLD when other causes of liver steatosis were excluded, such as viral hepatitis, hemochromatosis, or alcoholic liver disease.28 However, an elevated ALT is not the same as NAFLD, and when 160 patients undergoing bariatric surgery were studied by liver biopsies, levels of POP did not relate to liver steatosis, but rather to markers of liver inflammation.29 Liver inflammation in NAFLD has been denoted in non-alcoholic steato-hepatitis, a condition that is far more deleterious than NAFLD and that can progress to liver cirrhosis or hepatic cancer. Thus, while it is clear that POPs accumulate in the liver and have effects on lipid metabolism, it is at present unknown if background exposure in the general population is linked to NAFLD.

NON-LIPID SOLUBLE POPS: THE PFAS AND LIPOPROTEINS

Unlike the lipid-soluble POPs, PFAS compounds are mainly transported in the blood by albumin and accumulate in the liver and other protein-rich organs, but not adipose tissue.

Nevertheless, several studies have shown that subjects with elevated PFASs have increased total serum cholesterol levels.30-32 In a more detailed analysis, it was found that plasma PFAS levels were mainly related to blood lipids and apolipoproteins in intermediate-density lipoprotein, LDL, and HDL that contain apoC-III.33

An analysis of whole-blood mRNA expression levels showed, in a study sample contaminated with PFOA (the C8 study), negative links between PFOA levels and expression of genes of importance for cholesterol transport (NRIH2, NPC1, and ABCG1), providing evidence of molecular mechanisms by which PFASs could interfere with cholesterol metabolism.34 In a study using metabolomics, the PFASs perfluorononanoic acid (PFNA) and perfluoroundecanoic acid (PFUnDA) were strongly associated with multiple glycerophosphocholines and fatty acids including docosapentaenoic acid and

Table 2. Mechanisms whereby polychlorinated biphenyls could alter lipid handling in the liver

<table>
<thead>
<tr>
<th>Mechanism</th>
<th>Reference</th>
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<tbody>
<tr>
<td>Reduced expression of hepatic genes implicated in β-oxidation (PPAR-α and CPT1A/2) while increasing the expression of genes associated with lipid biosynthesis (FAS)</td>
<td>16</td>
</tr>
<tr>
<td>Increased expression of mRNA for DGAT1A, PPAR-γ, FAS, and SREBP (increased lipid synthesis)</td>
<td>17</td>
</tr>
<tr>
<td>Altered synthesis and secretion of VLDL</td>
<td>18</td>
</tr>
<tr>
<td>Increased expression of omega-hydroxylase P450, epoxygenase P450 and genes being related to insulin receptor signaling</td>
<td>19</td>
</tr>
<tr>
<td>Downregulated mRNA related to sphingolipid biosynthesis</td>
<td>19</td>
</tr>
<tr>
<td>Increased expression of FABP1 the lipogenic transcription factor SREBP1c and the lipid oxidation transcription factor PPAR-α</td>
<td>20</td>
</tr>
</tbody>
</table>

PPAR, peroxisome proliferator-activated receptor; FAS, fatty acid synthase; mRNA, messenger RNA; DGAT1A, diacylglycerol O-acyltransferase 1A; SREBP, sterol regulatory element-binding protein; VLDL, very-low-density lipoprotein; FABP1, fatty acid-binding protein 1.
docosahexaenoic acid, suggesting that PFAS might affect also other lipid species than those measured in the clinic.

**PFAS AND LIVER FAT**

A number of experimental studies in different settings have evaluated the effects of PFASs on liver metabolism. In mice, exposure to perfluorohexane sulfonate (PFHxS) and PFOS increased liver triglyceride content. Expression analysis in the liver indicated that PPAR-α and pregnane X receptor were involved in this liver steatosis formation. In another mice strain, PFOS induced steatosis in a dose-dependent manner. Expression analysis of the liver showed fatty acid translocase CD36 and lipoprotein lipase to be upregulated, and the rate of mitochondrial β-oxidation was reduced. Irreversible accumulation of lipid droplets in the liver was seen in zebrafish exposed to PFOS, most prominently in males. In chickens, exposure to PFOS resulted in a reduction of transcription of genes involved in fatty acid oxidation and PPAR-mediated transcription. In utero exposure in mice increased liver content of triglyceride, total cholesterol, and LDL. In parallel, transcription of cytochrome P4A14 for fatty acid oxidation, CD36 for hepatic fatty acid uptake, and apolipoprotein B100 and fibroblast growth factor 21 for hepatic export of lipids were altered.

Thus, different experimental models have repeatedly shown an effect of PFASs on liver and lipoprotein metabolism. The mechanistic findings regarding PFAS effects on lipid handling in the liver in the experimental studies are summarized in Table 3.

In humans, several studies have shown that elevated levels of PFASs are linked to altered levels of markers of liver function, such as ALP, ALT, AST, and GGT. However, we are still lacking studies clearly showing that background exposure to PFAS in the general population will induce NAFLD.

**LIPID-SOLUBLE POPS AND ATHEROSCLEROSIS**

The first evidences that lipid-soluble POPs might be involved in atherosclerosis development came from an experimental study showing that exposure of ApoE knock-out mice, a commonly used model of atherosclerosis, to PCB-77 accelerated atherosclerosis formation. A similar finding was later published using another model of atherosclerosis, the LDL-receptor knock-out mice.

| Table 3. Mechanisms whereby perfluoroalkyl substances could alter lipid handling in the liver |
|---------------------------------|-----------------|
| Mechanism | Reference |
| Increased expression of PPAR-α and pregnane X receptor | 31 |
| Increased expression of fatty acid translocase (CD36) and lipoprotein lipase | 32 |
| The rate of mitochondrial β-oxidation was reduced | 32 |
| Reduction of transcription of genes involved in fatty acid oxidation and PPAR-mediated transcription | 34 |
| Altered transcription of cytochrome P4A14 for fatty acid oxidation, CD36 for hepatic fatty acid uptake, and apolipoprotein B100 and fibroblast growth factor 21 for hepatic export of lipids | 35 |

PPAR, peroxisome proliferator-activated receptor.
Several years later, the first and, to our knowledge, only study on lipid-soluble POPs and atherosclerosis was published. In the population-based PIVUS study including around 1,000 participants all aged 70 years, using ultrasound measurement of the carotid artery in the area of the bifurcation, the occurrence of plaque was recorded, as well as the thickness of the intima-media (IMT) of a part of the vessel not including a plaque. Plaque was defined as a local 50% thickening of the intima-media complex (IM-GSM; see Fig. 1 for an example). In addition, the gray scale of the IM-GSM was analyzed yielding an indirect measure of lipid infiltration of the arterial wall. A low value of IM-GSM suggests a high degree of lipids in the IM-GSM, and this pattern is more closely related to future cardiovascular death than a high value. Also, plaque occurrence and an increased IMT have been shown to be associated with future cardiovascular disease (CVD). The main finding of that study was that levels of highly chlorinated PCBs (octa to deca) were related to all three of these atherosclerosis measurements independently of traditional risk factors, like blood pressure, LDL and HDL cholesterol, triglycerides, diabetes, or smoking. OC pesticides, such as \( p,p' \)-DDE, trans-nonachlordane and hexachlorobenzene were mainly related to IM-GSM, suggesting that the OC pesticides might be involved in the early lipid infiltration of the vascular wall, but that other factors are needed for plaque development. No consistent relationships were seen between the brominated flame retardant polybrominated diphenyl ether-47 and indices of carotid atherosclerosis.

Dioxins, furans and some PCBs bind to the aryl hydrocarbon receptor (AHR), and most of the known actions of these compounds are related to this receptor binding. It is of interest to note that when the ligand binding of the PCBs is calculated in the PIVUS study (the TEQ value), this value is not related to plaque occurrence, but only to IMT and IM-GSM. However, that absence of relationship vs plaque seems to be driven by the coplanar non-ortho-substituted PCBs (mainly PCB126 and 169), since a relationship was seen between the TEQ for the mono-ortho PCBs and plaque occurrence even though the mono-ortho PCBs contribute less to total TEQ than the coplanar non-ortho-substituted PCBs. Thus, it is likely that other properties of PCBs are also involved in atherosclerosis formation than simply the degree of AHR binding.

Fig. 1. Example of an atherosclerotic plaque detected by ultrasound of the carotid artery. The plaque is situated at the near wall in the bifurcation and indicated by the arrow. The plaque is echogenic and induces a shadowing of the far wall of the bifurcation.
Another interesting finding in the PIVUS study is that the strength of relationships between POPs and indices of carotid atherosclerosis was largely unaffected by adjustment for traditional risk factors for atherosclerosis, including HDL and LDL cholesterol and triglycerides. Similar results were obtained regardless of whether the POP levels used in the calculations were wet-weight or normalized for lipids. This indicates that the POPs might have direct effects on the vascular wall being independent from lipid levels and other cardiovascular risk factors.

**MECHANISMS WHEREBY LIPID-SOLUBLE POP COULD AFFECT ATHEROSCLEROSIS**

A number of effects of PCBs have been described that could contribute to atherosclerosis formation, apart from the effects on lipids. First, dioxin-like PCBs (DLPCBs), but not non-DLPCBs, elicited a proinflammatory response in cultured macrophages. This effect could be attenuated by blocking the Ah receptor. Also, other experimental studies have shown increased levels of proinflammatory cytokines and immunocompetent cells in response to PCB exposure. In humans, we have shown that PCB levels were related to the increased adhesion molecule 1 (ICAM-1), an adhesion molecule known to be involved in atherosclerosis formation. Also, in the experimental setting, PCB exposure increased ICAM-1 levels.

Second, several experimental studies have shown that PCBs increased reactive oxygen species and oxidative stress. Similar findings have also been reported by us in humans. In that study, PCBs and OC pesticides were related to circulating levels of oxidized LDL and conjugated dienes. Furthermore, PCBs were significantly associated with the glutathione ox/redox ratio in an inverse way. None of the POPs were related to total antioxidative capacity. Third, a proper release of nitric oxide (NO) is crucial for the maintenance of a normal arterial wall. Exposure of human umbilical vein endothelial cells (HUVECs) to PCB-118 attenuated insulin-induced NO production and activity of endothelial NO synthase. Furthermore, PCB104 exposure of *ex vivo* rat aortic attenuated acetylcholine-mediated vasodilation, an NO-dependent process. Fourth, apoptosis of endothelial cells is one mechanism in atherosclerosis formation. *In vitro*, exposure to PCB118 increased apoptosis of HUVECs. A summary of these mechanisms is given in Table 4.

**PFAS AND ATHEROSCLEROSIS**

Lin and co-workers published in 2013 that PFOS levels were related to IMT in a sample of young adults. This relationship was most evident in females. The same group later published that circulating endothelial microparticles and platelet microparticles could be involved in the relationship between PFOS and IMT.

<table>
<thead>
<tr>
<th>Mechanism</th>
<th>Reference</th>
</tr>
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<tbody>
<tr>
<td>Induce inflammation by binding to AHR</td>
<td>39,40,42</td>
</tr>
<tr>
<td>Increased adhesion molecule 1</td>
<td>43,44</td>
</tr>
<tr>
<td>Increased reactive oxygen species and oxidative stress</td>
<td>42,45-48</td>
</tr>
<tr>
<td>Impair activity of endothelial nitric oxide synthase</td>
<td>45,49</td>
</tr>
<tr>
<td>Apoptosis of endothelial cells</td>
<td>46</td>
</tr>
</tbody>
</table>

AHR, aryl hydrocarbon-receptor.
In the PIVUS study, a cross-sectional analysis revealed that long-chained PFASs, especially PFUnDA, were related to plaque occurrence, but that this association only existed in women. In a longitudinal analysis of the same cohort over 10 years, the change in all of the evaluated PFASs (perfluoroheptanoic acid, PFNA, perfluorodecanoic acid, PFUnDA, PFHxS, PFOS, PFOA, and perfluorooctane sulfonamide) were more or less related to the change in IMT. In the latter study, no differences between men and women were seen. In both of these studies the relationships were significant also after adjustment for traditional risk factors, like blood pressure, LDL and HDL cholesterol, triglycerides, diabetes or smoking. As far as we know, there are no experimental studies on PFASs and atherosclerosis progression. An overview of the relationships between POPs and carotid artery plaques is given in Fig. 2.

**MECHANISMS WHEREBY PFAS COULD AFFECT ATHEROSCLEROSIS**

Apart from its effect on lipids, the PFASs by activation of PPAR-α and -γ receptors also could affect fat distribution and insulin action. It is of interest to note that PPAR-γ agonists used as pharmaceutical drugs, the drug-class glitazones, have been reported to reduce IMT in clinical trials. PFASs has also been related to a number of impairments in the immune system, such as T-cell-dependent antibody response and impairment in B-cell/plasma cell function.

**POPS AND CVD**

One way to investigate the effect of POPs on disease is by studying disasters. In 1976 a plant in Soveso in Northern Italy exploded and thereby exposed a small town to a potent dioxin, TCDD, a by-product in the chemical production. In a 25-year follow-up on mortality, increased mortality from CVDs was seen during years 5 to 10 following the explosion. Thereafter the mortality rate from CVD declined to levels noted in nearby, non-contaminated areas.

**Fig. 2.** Relationships between some selected POP and occurrence of carotid artery plaque in the prospective study of the vasculature in Uppsala seniors study. The odds ratios are given for one standard deviation change in the POPs in order to make the estimates comparable. The data used in this figure are originally given in references 47 and 58.

POPs, persistent organic pollutant; PFUnDA, perfluoroundecanoic acid; OCDD, octachlorodibenzo-p-dioxin; BDE47, polybrominated diphenyl ether-47; p,p'-DDE, p,p'-dichlorodiphenyl dichloroethylene.
Another way to study effects of POPs on disease is by use of occupational studies. In a meta-
alysis of 36 cohorts from 13 countries, including 21,863 workers being exposed for TCDD
and followed for >20 years, the IARC international cohort was formed. During the follow-up,
a significant increase in incident myocardial infarction and a trend towards an increased
incidence of stroke were seen.63 In US veterans involved in the spraying of the herbicide Agent
Orange, contaminated with TCDD, an increased risk of incident myocardial infarction was
seen over 30 years of follow-up.64 Thus, data from a disaster and occupational data support
that exposure to high levels of the potent dioxin TCDD could be linked to future CVD.

Another way to study these relationships is by ecological studies. By this technique it has
been shown that subjects living close to a waste site contaminated with POP showed higher
rates of CVDs than those who did not.65,66 Also, in studies in which the dietary intake of PCB
was estimated, links between PCB exposure and CVD have been found.67-69

Most individuals are exposed to the background levels measured in the majority of subjects in
industrialized countries. Therefore, an important study was published in 2007 using publicly
available data from the US-based NHANES study. Ha et al.70 showed in this cross-sectional
study that both PCBs and OC pesticides were associated with prevalent CVD in women only,
but dioxins were associated with CVD in both sexes. These relationships were seen despite
adjustment for traditional risk factors, including lipids, but it was of interest to note that in
another study POP concentrations in HDL were more closely associated with CVD than POPs
in other lipoproteins.71

Since cross-sectional studies could be subject to reverse causation, in the PIVUS study we could
use a longitudinal design to show that both PCBs and OC pesticides were linked to incident
stroke over a 5-year follow-up period.72 We also found that highly chlorinated PCBs, but not
OC pesticides, were related to all-cause mortality during a 10-year follow-up period.73 For
example, one standard deviation increase in PCB206 increased the mortality risk by 47% (95%
confidence interval, 19%-81%). In a further analysis of the cause of death, it was found that this
relationship mainly was driven by death due to CVDs. In that study, we used measurements of
POPs performed at age 70 years and at age 75 years to increase the precision in the analysis, as
compared to the more common approach in cohort studies which the exposure is measured
only once at the baseline. The relationships persisted also after adjustment for traditional risk
factors, including lipids. In this case, in opposition to the observations regarding POPs and
carotid artery atherosclerosis, the risk of cardiovascular mortality was attenuated, but still
significant, following adjustment for traditional risk factors, suggesting that a part of the effect
of especially highly chlorinated PCBs is mediated by traditional risk factors. When a summary
measure of the DLPCBs (PCBs 105, 118, 156, 157, and 189) was compared with a summary
measure of the non-DLPCBs, both summary measures were associated with cardiovascular
mortality, suggesting that the effects of PCBs are not only mediated by the AHR. We also noted
that mortality risk increase associated with the highly chlorinated PCBs declined at high levels
of the PCBs, suggesting that the increased risk is mainly seen at the concentrations seen in
the majority of individuals in the population. Three OC pesticides, including p,p’-DDE, and
the brominated flame retardant PBD47 were also evaluated, but did not show any significant
associations with all-cause or cardiovascular mortality.

In one study linking PFAS levels to prevalent CVD in a cross-sectional fashion in the NHANES
database, a summary measure of several PFAS was associated with prevalent CVD.74 Also,
another evaluation of NHANES data found PFOA to be linked to prevalent CVD.75 Thus,
there are evidences that both lipid-soluble POPs, as well as PFAS, could be involved in the development of CVD.

CONCLUSION

Taken together, several lines of evidence support the view that POPs of different chemical classes could be linked to lipid abnormalities, carotid atherosclerosis and overt CVD, like myocardial infarction and stroke.

However, some knowledge gaps should be acknowledged. First, the number of cohort studies with longitudinal data regarding atherosclerosis development and incident cases of CVD are limited. Furthermore, experimental studies on the effect of PFASs on atherosclerosis are warranted to support the epidemiological data.

Most of the major lipid-soluble POPs are banned from production and therefore the levels in humans and the environment are declining. However, dietary intake from fat fish and meat is still a problem, and especially intake of fat fish from contaminated areas should be kept to a minimum. Also, PFASs are derived from fish and meat, but in this case many PFASs are still produced. Since PFAS substances have many warranted properties, intense actions have to be carried out to develop alternatives without adverse health effects. Regulatory authorities dealing with chemicals could well play a more active role in this process.

REFERENCES


https://doi.org/10.12997/jla.2020.9.e25


PUBMED | CROSSREF

PUBMED | CROSSREF

PUBMED | CROSSREF

47. Lind PM, van Bavel B, Salihovic S, Lind L. Circulating levels of persistent organic pollutants (POPs) and carotid atherosclerosis in the elderly. Environ Health Perspect 2012;120:38-43. 
PUBMED | CROSSREF

PUBMED | CROSSREF

PUBMED | CROSSREF

PUBMED | CROSSREF

PUBMED | CROSSREF

PUBMED | CROSSREF

PUBMED | CROSSREF

PUBMED | CROSSREF

PUBMED | CROSSREF

PUBMED | CROSSREF

PUBMED | CROSSREF

PUBMED | CROSSREF

59. Lind PM, Salihovic S, Stubleski J, Kärnman A, Lind L. Changes in plasma levels of perfluoroalkyl substances (PFASs) are related to increase in carotid intima-media thickness over 10 years - a longitudinal study. Environ Health 2018;17:59. 
PUBMED | CROSSREF

PUBMED | CROSSREF
PUBMED | CROSSREF

PUBMED | CROSSREF

PUBMED


PUBMED | CROSSREF

PUBMED | CROSSREF

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