Association between environmental contaminants and health outcomes in indigenous populations of the Circumpolar North

Kavita Singh¹, Peter Bjerregaard² and Hing Man Chan³*

¹Department of Biology, University of Ottawa, Ottawa, ON, Canada; ²Department of Health, Centre for Health Research in Greenland, Greenland Government and University of Greenland, Nuuk, Greenland; ³Canada Research Chair in Toxicology and Environmental Health, Center for Advanced Research in Environmental Genomics, University of Ottawa, Ottawa, ON, Canada

Background. Since the 1990s, research has been carried out to monitor environmental contaminants and their effects on human health in the Arctic. Although evidence shows that Arctic indigenous peoples are exposed to higher levels of contaminants and do worse on several dimensions of health compared with other populations, the contribution of such exposures on adverse outcomes is unclear.

Objective. The purpose of this review is to provide a synopsis of the published epidemiological literature that has examined association between environmental contaminants and health outcomes in Arctic indigenous populations.

Design. A literature search was conducted in OVID Medline (1946-January 2014) using search terms that combined concepts of contaminant and indigenous populations in the Arctic. No language or date restrictions were applied. The reference lists of review articles were hand-searched.

Results. Of 559 citations, 60 studies were relevant. The studies fell under the following categories: paediatric (n=18), reproductive health (n=18), obstetrics and gynaecology (n=9), cardiology (n=7), bone health (n=2), oncology (n=2), endocrinology (n=2) and other (n=2). All studies, except one from Arctic Finland, were either from Nunavik or Greenland. Most studies assessed polychlorinated biphenyls (n=43) and organochlorine pesticides (n=29). Fewer studies examined heavy metals, perfluorinated compounds, or polybrominated diphenyl ethers. Details of study results for each health category are provided.

Conclusions. It is difficult to make conclusive statements about the effects of environmental contaminants on health due to mixed results, small number of studies and studies being restricted to a small number of regions. Meta-analytical synthesis of the evidence should be considered for priority contaminants and health outcomes. The following research gaps should be addressed in future studies: association of contaminants and health in other Arctic regions (i.e. Inuvialuit Settlement Region, Nunavut, Nunatsiavut, Alaska, European North and Russian North); assessment of contaminants on chronic diseases; inclusion of clinical endpoints in assessments; and assessment of the emerging contaminants of perfluorinated compounds and polybrominated diphenyl ethers.

Keywords: epidemiology; review; environment; human health; polychlorinated biphenyls; pesticides

*Correspondence to: Hing Man Chan, Canada Research Chair in Toxicology and Environmental Health, Center for Advanced Research in Environmental Genomics, University of Ottawa, 30 Marie Curie, Ottawa, ON-K1N 6N5, Canada, Email: laurie.chan@uottawa.ca

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by Arctic populations thus leads to direct contaminant exposure. The presence of contaminants in the North has garnered the attention of researchers. Since the 1990s, multidisciplinary international projects have been implemented to monitor contaminants and potential impacts on human health in the Arctic (1). The most important initiative, the Arctic Monitoring Assessment Programme (AMAP), includes all Arctic countries and had led to a series of reports detailing pollution and climate change issues (2–4).

Studies have shown that indigenous populations in the Arctic have higher body burden of contaminants than other populations. Donaldson et al. reported higher concentrations of heavy metals and persistent organic pollutants in Inuit mothers from Inuvik compared with Dene/Metis and non-aboriginal women (5). High levels were also measured in Inuit mothers from Nunavik and the Baffin region of Nunavut, although levels decreased from 1992 to 2007 (5). From the Adult Inuit Health Survey, Laird et al. reported several-fold higher contaminant levels in Canadian Inuit compared with the general Canadian population (6). In the Russian North, contaminant levels were measured in blood, cord blood, and breast milk of indigenous women, and blood of adult indigenous populations and controls residing in urban locations (3). Mothers from the Chukotsky District had the highest contaminant concentrations in blood and breast milk. Overall, blood contaminant levels in indigenous populations of Arctic Russia were similar to those of coastal Greenland and Northern Canada (3).

Many of the health issues faced by Arctic populations are related to the shift from traditional to modern lifestyles, which result in more sedentary behaviours and consumption of higher-fat content, nutrient-poor market foods. The shift in lifestyle has resulted in a corresponding shift from infectious diseases to chronic, non-communicable diseases such as diabetes, cardiovascular disease and cancer (3,7–9). The prevalence of diabetes among the Inuit in Canada, for instance, has historically been below the national average, but has now increased to an equivalent level (10). Chronic disease risk factors, such as obesity and smoking, are prevalent among Northern communities. In 2009–2010, 58.3% of Inuit adults 18 years of age or older in Canada were overweight or obese, compared with 51.9% among the non-aboriginal population (10). Furthermore, 59.6% of Inuit adults reported being physically inactive during leisure time (49.7% among non-aboriginal populations), 78.4% ate less than the recommended number of servings of fruits and vegetables per day, and 44.4% smoked tobacco (16% among non-aboriginal populations) (10).

While it is clear that Arctic populations are exposed to higher levels of environmental contaminants and fare worse on certain dimensions of health than other populations, the resulting impact of these exposures on health are still ambiguous. Contaminants do not exist in isolation — they are but one additional risk factor among a plethora of other factors, such as diet, smoking, genetic predisposition and socioeconomic status, that contribute to disease. Isolating the effects of contaminants from these other contributors can be difficult in epidemiological studies of small populations (5). Nonetheless, the ongoing inquiry into the adverse health effects of contaminants is vital so that research methods undergo refinement to detect small, but relevant, associations and scientifically based messages of exposure and strategies for mitigation are conveyed to the populations at risk.

Because the Arctic indigenous peoples have distinct cultural practices, diet and socioeconomic factors that make them vulnerable to contaminant exposure and adverse health outcomes, the purpose of this review is to provide a synopsis of the published epidemiological research, available to date, that has examined association between environmental contaminants and health outcomes in these populations. The primary aim is to identify health topics that have received greater research attention and areas where more research is needed. Donaldson et al. provided an overview of the health effects of contaminants, though not restricted to Arctic populations (5). This review updates this previous work. In addition, this review provides a systematic assessment of the literature in Arctic populations and graphical representations to show research gaps.

Methods
A comprehensive search of the published literature was conducted in OVID Medline (1946-January 2014) using search terms that combined the concepts of contaminant and indigenous Arctic populations. To describe Arctic indigenous populations, we included the following search terms: Inuit, Dene, Kalaallit, Yupik, Buryat, Chukchi, Evenk, Khanty, Koriak, Koryak, Nenet, Sami, Yukaghir, Mansi, Naganian and similar terms with variations of spelling. No language or date restrictions were applied. The titles and abstracts of all citations yielded by the searches were reviewed. Primary studies that examined the effect of at least one environmental contaminant on any type of health outcome in humans were retained and included in the review. The reference lists of selected review articles were also hand-searched for relevant primary studies. Studies reporting body burden, intake of contaminants, or health outcomes only were not included in this review.

The studies were organized into broad health categories. In addition, studies were tabulated according to location and environmental contaminant. Basic data characteristics, such as study design, sample size, contaminant exposure level and overall results, were extracted for individual studies and presented in tabular format.
Major cohort studies on the health effects of polychlorinated biphenyls (PCBs) and mercury have been conducted in the Faroe Islands (11–13). Based on cultural and geographical differences, they are not included in this review, which focuses on indigenous populations of the circumpolar Arctic countries. In addition, several studies on the health effects of contaminants in Norway and Russia (14–18) have been conducted, but they have not been included in this review because they were not limited to the indigenous populations of those regions.

**Results**

The Medline search yielded a total of 559 citations. Of these, and the references hand-searched from review articles, 60 primary studies were deemed to be relevant for this review (i.e. these studies included an evaluation of at least one association between an environmental contaminant and a health outcome in an indigenous population in the Arctic). Other excluded studies primarily measured levels of environmental contaminants in humans but did not link such measurements with health outcomes. The studies fell under the following broad categories: paediatric, reproductive health, obstetrics and gynaecology, cardiology, bone health, oncology, endocrinology and other. Studies that examined health outcomes of environmental contaminants in children under the age of 18 years of age were classified under the paediatric category and omitted from the other categories. Similarly, studies that examined health outcomes in pregnant women were classified under the obstetrics and gynaecology category and omitted from other categories (e.g. assessment of thyroid function in pregnant women was classified under obstetrics and gynaecology rather than endocrinology).

Figure 1 depicts the number of studies falling under each health category. Most studies examined associations between contaminants and health outcomes in paediatrics (N = 18) and on reproductive health outcomes (N = 18). Subsequent categories were obstetrics and gynaecology (N = 9) and cardiology (N = 7). Only 2 studies were found in each of bone health, oncology and endocrinology. In addition, 2 studies that examined markers of oxidative stress were classified in the other category.

All studies were from either Nunavik or Greenland, except for one study from Arctic Finland (Fig. 2).

The majority of paediatric studies examined Inuit from Nunavik whereas all reproductive health studies examined Inuit from Greenland.

As shown in Fig. 3, most studies examined the adverse health impacts of PCBs (N = 43) and organochlorine pesticides (N = 29). Smaller number of studies examined heavy metals (Hg, N = 20; Pb; N = 9; Cd, N = 2), perfluorinated compounds (N = 4), polybrominated diphenyl ethers (PBDEs) (N = 1) and other contaminants including octachlorostyrene, dioxin-like compounds and unspecified persistent organic pollutants (N = 5). Aside from cardiology, PCBs were examined by the largest number of studies in all health categories. Organochlorine pesticides or heavy metals fared second.

**Paediatric**

Paediatric studies have examined associations between PCBs or organochlorine pesticides with infections and immune status (19–22), neurological function (23–26), indicators of behaviour (27–29) and thyroid function (30) (Table I). Studies have also looked at heavy metals (i.e. Hg or Pb) and their effects on blood pressure and heart rate variability (31), neurological function (23–26,32–34) and behaviour (27,29,35,36). Most studies were prospective cohorts of mother–child pairs that followed children from birth to infants or childhood. Sample sizes ranged from 10 to 400. Contaminant levels were measured in maternal blood, cord blood, breast milk and/or child blood and mercury hair levels were measured in some studies. Most analyses adjusted for several demographic (e.g. age, gender), lifestyle (e.g. smoking) and other contaminant exposures.

**Infections and immune system**

For infection-related outcomes studies presented mixed results. One study found no association between PCBs and organochlorine pesticides with otitis media (19). However, Dallaire et al. found that cord PCB-153 was associated with higher incidence of acute otitis media (adjusted RR = 1.37, 95% CI: 1.20–1.55 for most exposed compared with least exposed) and lower respiratory tract infections (LRTI) (adjusted RR = 1.44, 95% CI: 1.20–1.72) (20). In addition, maternal PCB-153 was positively associated with LRTI in the first 6 months of life (adjusted RR = 1.68, 95% CI: 1.00–2.81, for 3rd exposure quartile compared with least exposed) and gastrointestinal (GI) infections at 12 months (adjusted RR = 1.59, 95% CI: 1.01–2.49, for 3rd exposure quartile compared with least exposed) (21). In the same study, maternal p,p'-dichlorodiphenyldichloroethylene (p,p'-DDE) was found to be associated positively with upper respiratory tract infections (URTIs), otitis media, and all infections during the first 6 months of life and URTI and GI infection at 12 months (21). Dewailly et al. found that organochlorine pesticides were associated with increased risk of acute otitis media but not with bronchopulmonary diseases (22).

![Fig. 1. Studies by health category.](Image)
Behaviour

Boucher et al. observed a higher incidence of attention deficit hyperactivity disorder (ADHD) in children 11 years of age exposed to mercury prenatally and among those with higher levels of blood lead (27). No association was seen between ADHD and PCB-153 (27). However, other studies found that PCB-153 was associated positively with inattention and non-elicited activity in infants aged 11 months (28) and with unhappiness and anxiety in children aged 5 years (29). Child blood lead levels have been observed to be associated with greater impulsivity (29), irritability (29) and activity (36). Plusquellec et al. also found a positive association with inattention (29), but this was not detected in other studies (27,36). Prenatal exposure to lead was associated with greater frenetic activity and off-task duration in infants (35).

Neurological

No association was detected between PCB-153 and visual brain development, but cord mercury and lead levels were associated with certain visual evoked potentials (i.e. N75 amplitude, N75 latency and N150 latency) (23). Saint-Amour et al. found that child plasma PCB-153 and cord and child blood mercury levels were associated with alterations in visual brain processing, as assessed by visual evoked potentials (33). Child plasma levels of PCB-153 have also been significantly associated with slower reaction times (24) and an increase in transversal sway.

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Fig. 2. Studies by health category and location.

Fig. 3. Studies by contaminant.

*OCPs – e.g. p,p'-DDE, DDT, HCB, PCP.
**PFCs – e.g. PFOA, PFOS.
***Other – octachlorostyrene, dioxin-like compounds, POPs (specific compounds unspecified).

Cd = cadmium; DDE = dichlorodiphenyldichloroethylene; DDT = dichlorodiphenyltrichloroethane; HCB = hexachlorobenzene; Hg = mercury; OCPs = organochlorine pesticides; Pb = lead; PBDEs = polybrominated diphenyl ethers; PCBs = polychlorinated biphenyls; PCP = pentachlorophenol; PFCs = perfluorinated compounds; PFOA = perfluorooctanoic acid; PFOS = perfluorooctanesulfonate; POPs = persistent organic pollutant.
| Study            | Contaminant          | Outcome                        | Population                                                                 | Results*                        |
|------------------|----------------------|--------------------------------|---------------------------------------------------------------------------|---------------------------------|
| **Infections**   |                      |                                |                                                                           |                                 |
| Jensen (19)      | PCBs and OCPs        | Otitis media                   | Mother–child pairs (n = 400) and children 4–10 years of age at follow-up (n = 223) (participation rate: 56%) | No association                  |
| Dallaire (20)    | PCBs                 | Acute respiratory infection    | Children 0–5 years of age (n = 343) (participation rate: 70%)            | Cord PCB-153                    |
|                  |                      |                                |                                                                           | Acute otitis media: RR = 1.37, 95% CI: 1.20–1.55                           |
|                  |                      |                                |                                                                           | LRTI: RR = 1.44, 95% CI: 1.20–1.72                                       |
|                  |                      |                                |                                                                           | URTI or hospitalization: No association                                   |
| Dallaire (21)    | PCBs and p,p′-DDE    | Acute infections               | Infants during the first 12 months of life (n = 199)                      | Maternal PCB-153                |
|                  |                      |                                |                                                                           | LRTI (first 6 months): RR = 1.68, 95% CI: 1.00–2.81 (3rd exposure quartile) |
|                  |                      |                                |                                                                           | GI infection (12 months): RR = 1.59, 95% CI: 1.01–2.49 (3rd exposure quartile) |
|                  |                      |                                |                                                                           | Maternal p,p′-DDE               |
|                  |                      |                                |                                                                           | URTI (first 6 months): RR = 1.56, 95% CI: 1.05–2.33 (2nd exposure quartile) |
|                  |                      |                                |                                                                           | URTI (12 months): RR = 1.34, 95% CI: 1.00–1.78 (2nd exposure quartile)     |
|                  |                      |                                |                                                                           | Otitis media (first 6 months): RR = 1.83, 95% CI: 1.09–3.07 (3rd exposure quartile) |
|                  |                      |                                |                                                                           | All infections (first 6 months): RR = 1.33, 95% CI: 1.03–1.73 (3rd exposure quartile) |
|                  |                      |                                |                                                                           | GI infection (12 months): RR = 1.59, 95% CI: 1.03–2.47 (2nd exposure quartile) |
| Dewailly (22)    | PCBs and OCPs        | Infections and immune status   | Newborns followed up to 12 months of age (n = 171)                        | Child PCB or p,p′-DDE: No association                                   |
|                  |                      |                                |                                                                           |                                 |
|                   |                      |                                |                                                                           |                                 |
| **Behavioural**  |                      |                                |                                                                           |                                 |
| Boucher (27)     | PCBs, Hg and Pb      | ADHD                           | Children followed from birth to 11 years of age (n = 279) (participation rate: 95%) | Cord Hg                         |
|                  |                      |                                |                                                                           | Attention problems: Positive association (β = 0.13, 95% CI: 0.00–0.25)      |
|                  |                      |                                |                                                                           | Disruptive Behaviour Disorders score:                                    |
|                  |                      |                                |                                                                           | OR = 2.87, 95% CI: 1.04–7.94 (ADHD-inattentive type, 3rd exposure tertile) |
|                  |                      |                                |                                                                           | OR = 2.92, 95% CI: 1.07–8.04 (ADHD-hyperactive impulsive type, 3rd exposure tertile) |
| Study                  | Contaminant                | Outcome             | Population                          | Results*                                                                 |
|-----------------------|---------------------------|---------------------|-------------------------------------|--------------------------------------------------------------------------|
| Verner (28)           | PCBs                      | Attention and activity | Infants followed from birth to 11 months of age (n = 168) | Child blood Pb                                                          |
|                       |                           |                     |                                     | • Externalizing problems: Positive association (β = 0.14, 95% CI: 0.01–0.26) |
|                       |                           |                     |                                     | • Disruptive Behaviour Disorders score:                                   |
|                       |                           |                     |                                     |   OR = 5.52, 95% CI: 1.38–22.12 (ADHD-hyperactive impulsive type, 3rd exposure tertile) |
|                       |                           |                     |                                     | PCB-153: No association                                                 |
| Plusquellec (29)      | PCBs, Hg and Pb           | Behavioural indicators | Children followed from birth to 5 years of age (n = 110) | Child blood Pb                                                          |
|                       |                           |                     |                                     | • Inattention: Positive association (Spearman's correlation = 0.205)        |
|                       |                           |                     |                                     | • Non-elicited activity: Positive association (Spearman's correlation = 0.182 at 11 months of age) |
|                       |                           |                     |                                     | Cord PCB-153                                                            |
|                       |                           |                     |                                     | Hg: No association                                                      |
| Plusquellec (35)      | Pb                        | Behavioural function | Infants 11 months of age (n = 169)   | Child blood Pb                                                          |
|                       |                           |                     |                                     | • Impulsivity: Positive association (β = 0.20)                           |
|                       |                           |                     |                                     | • Irritability: Positive association (β = 0.20)                           |
|                       |                           |                     |                                     | • Inattention: Positive association (β = 0.21)                           |
| Fraser (36)           | Pb                        | Motor function and behaviour | Children 5 years of age (n = 110)    | Child blood Pb                                                          |
|                       |                           |                     |                                     | • Impulsivity: Positive association (Pearson correlation = 0.25)           |
|                       |                           |                     |                                     | • Activity: Positive association (Pearson correlation = 0.25)              |
|                       |                           |                     |                                     | No association with attention level                                      |
| Neurological          | PCBs, Hg and Pb           | Visual brain development | Children followed from birth to 10–13 years of age (n = 172) | Cord Hg                                                                 |
| Ethier (23)           |                           |                     |                                     | • N75 amplitude at 95% contract level: Positive association (β = 0.206)    |
|                       |                           |                     |                                     | • N75 latency at 12% contrast level: Positive association (β = 0.285)      |
|                       |                           |                     |                                     | Cord Pb                                                                 |
|                       |                           |                     |                                     | • N150 latency: Positive association (β = 0.238, 0.209, 0.251 at 95%, 12% and 4% contrast levels respectively) |
|                       |                           |                     |                                     | PCB-153: No association                                                  |
| Study               | Contaminant         | Outcome                          | Population                          | Results*                                                                                     |
|--------------------|---------------------|----------------------------------|-------------------------------------|----------------------------------------------------------------------------------------------|
| Boucher (24)       | PCBs               | Response inhibition error monitoring | Children followed from birth to a mean age of 11 years (n = 196) | - Child plasma PCB-153<br>  - Reaction times: Positive association (i.e. slower times) \( (\beta = 0.18 \text{ for go trials}) \)<br>  - Amplitudes of \( P_a \) and \( P_c \) response-related potentials: Inverse association (\( \beta = -0.16 \) and \(-0.20 \) respectively)<br>  - Cord Pb:<br>  - Correct responses: Inverse association (i.e. fewer correct responses) (\( \beta = -0.21 \) and \(-0.17 \) for correct go and no-go responses respectively)<br>  - Child blood Pb:<br>  - Correct responses on no-go trials (false alarms): Inverse association (more false alarms) \( (\beta = -0.16) \)<br>  - P3 amplitudes: Inverse association (\( \beta = -0.16 \) and \(-0.23 \) for go and no-go trials respectively) |
| Boucher (25)       | PCBs and Hg        | Information processing            | Children followed from birth to 11 years of age (n = 118) | - Cord PCB: No association with sample as a whole<br>  - P3b amplitude in subgroup of children breast-fed for > 3 months: Inverse association \( (\beta = -0.32) \)<br>  - Cord Hg:<br>  - Reaction times: Positive association (i.e. slower time) \( (\beta = 0.15) \)<br>  - False alarms: Inverse association (i.e. fewer false alarms) \( (\beta = -0.21) \)<br>  - N1 latency: Positive association \( (\beta = 0.29) \)<br>  - N1 amplitude: Inverse association \( (\beta = -0.32) \) |
| Boucher (32)       | Pb                  | Working memory                    | Children 5 years of age \( (n = 104) \) or 11 years of age \( (n = 201) \) (participation rate: 26% for ERP at 5 years and 55% for ERP at 11 years) | - Cord Pb (5 years)<br>  - P3b amplitude: Inverse association \( (\beta = -0.38) \)<br>  - Child blood Pb (5 years)<br>  - P3b latency: Positive association \( (\beta = 0.37) \)<br>  - Pb (11 years): No association |
| Saint-Amour (33)   | PCBs and Hg        | Visual brain processing           | Children followed from birth to 5-6 years of age \( (n = 102) \) | - Child plasma PCB-153<br>  - P100 latency at 95% contrast: Positive association \( (\beta = 2.50) \)<br>  - N150 latency at 12% contrast: Positive association \( (\beta = 5.58) \)<br>  - N75-P100 amplitude at 95% contrast: Inverse association \( (\beta = -3.74) \)<br>  - Cord Hg:<br>  - P100 latency at 30% contrast: Positive association \( (\beta = 3.34) \)<br>  - Child blood Hg:<br>  - N75 early latency at 95% and 30% contrasts: Inverse association \( (\beta = -3.90 \text{ and } -3.18, \text{ respectively}) \)<br>  - P100 latency at 95% and 30% contrasts: Inverse association \( (\beta = -3.26 \text{ and } -3.94, \text{ respectively}) \)
Table I (Continued)

| Study       | Contaminant                           | Outcome                          | Population                                | Results*                                                                 |
|-------------|---------------------------------------|----------------------------------|-------------------------------------------|-------------------------------------------------------------------------|
| Després (26)| PCBs, Hg and Pb                       | Neuromotor functions             | Children followed from birth to pre-school (n = 110) | Child plasma PCB-153
  - Sway oscillations: Positive association ($\beta = 0.22$ for transversal sway)
  - Child blood Hg
  - Tremor: Positive association ($\beta = 0.20$)
  - Child blood Pb
  - Reaction time: Positive association (i.e. slower time) ($\beta = 0.24$)
  - Sway oscillations: Positive association ($\beta = 0.24, 0.22, 0.26$ for velocity, sagittal and transversal sway)
  - Movement irregularity: Positive association ($\beta = 0.22$)
  - Coherence between hands: Inverse association ($\beta = -0.29$)
  - Synkinesis: Positive association ($\beta = 0.23$)
  - Tremor: Positive association ($\beta = 0.24$) |
| Weihe (34)  | Hg                                    | Neurobehavioural performance     | Children followed from birth to 7–12 years of age (n = 21) and children 7–12 years of age (n = 22) | Maternal hair Hg
  - Hand-eye coordination (error score): Positive association ($r = 0.44$)
  - Peak latencies on brainstem auditory evoked potentials prolonged at higher exposure levels when data combined with other cohorts (Faroes and Madeira) |
| Cardiovascular and endocrine
Valera (31)  | Hg                                    | Blood pressure and heart rate variability | Children followed from birth to 11 years of age (n = 226) | Child blood Hg
  - HRV – low frequency: Inverse association ($\beta = -0.24$)
  - HRV – SDNN: Inverse association ($\beta = -0.28$)
  - HRV – SDANN: Inverse association ($\beta = -0.32$)
  - HRV – CVRR: Inverse association ($\beta = -0.06$)
  - Blood Pressure: No association |
| Sandau (30) | PCBs, PCP and octachlorostyrene       | Thyroid function                 | Newborns (n = 10)                           | Cord PCP
  - $T_3$, TBG and $fT_4$: Inverse association ($r = -0.55, -0.44, -0.51$ respectively)
  - Cord $\Sigma$PCBs and $\Sigma$PCB hydroxylated metabolites
  - TSH: Inverse association ($r = -0.46$ and $-0.45$ respectively)
  - Sum of all cord chlorinated phenolic compounds
  - $T_3$ and $fT_4$: Inverse association ($r = -0.48$ and $-0.47$ respectively) |

ADHD = attention deficit hyperactivity disorder; CI = confidence interval; CVRR = coefficient of variation of R-R intervals; DDE = dichlorodiphenyldichloroethylene; ERP = event-related potential; $fT_4$ = free thyroxine; GI = gastrointestinal; HCB = hexachlorobenzene; Hg = mercury; HRV = heart rate variability; LRTI = lower respiratory tract infection; OCPs = organochlorine pesticides; OR = odds ratio; Pb = lead; PCBs = polychlorinated biphenyls; PCP = pentachlorophenol; RR = relative risk; SDANN = standard deviation of R-R intervals measured over 5 min periods; SDNN = standard deviation of R-R intervals; $T_3$ = triiodothyronine; TBG = thyroid-binding globulin; TSH = thyroid-stimulating hormone; URTI = upper respiratory tract infection

*Adjusted estimates are presented where available. Presented estimates are statistically significant at $p \leq 0.05$ level.
oscillations (26). Lead levels in cord and child blood have been associated with fewer correct responses on go and no-go trials (24) and adverse neuromotor functions (26). Mercury has also been found to adversely affect information processing (e.g. slower reaction times, incorrect responses) (25), increase tremors (26) and hand–eye coordination error score (34).

Cardiovascular and endocrine
Only one study assessed the effect of mercury on cardiovascular outcomes in children who were followed from birth to 11 years of age (31). No association was found between mercury levels and blood pressure. However, child mercury level was associated with certain measures of heart rate variability. A small study in newborns (n = 10) evaluated the effect of PCB, pentachlorophenol (PCP) and octachlorostyrene exposure on thyroid function (30). PCP, ΣPCBs and ΣPCB hydroxylated metabolites were found to be inversely associated with thyroid hormones.

Reproductive health
Studies of reproductive health have primarily examined the effects of PCBs and organochlorine pesticides on oestrogen, androgen or aryl hydrocarbon receptor activities (37–42), fertility and markers of male reproductive function (43,44), sperm deoxyribonucleic acid (DNA) damage and apoptotic markers (45,46), epididymal and accessory sex gland functions (47), reproductive hormone levels (48) and sperm Y:X ratio (49) (Table II). Sample sizes range from 37 to 598. Several studies analyzed a cohort of Greenlandic Inuit men from the INUENDO project, which also recruited cohorts of men from Warsaw, Kharkiv and Swedish fishermen for comparisons. The results presented in Table II are for the Inuit cohort only.

The effects of PCB-153 on reproductive outcomes have been mixed in the published literature. Some studies have found statistically significant inverse associations with sperm volume, progressive sperm and neutral a-glucosidase activity in seminal plasma (an epididymal marker) (43,47) and statistically significant positive associations with luteinizing hormone (43,48). However, no associations have been found with time to conceive, apoptotic markers, sperm chromatin integrity, other reproductive hormones, sperm Y:X ratio, or fertility (43–49). Studies also present mixed results for p,p′-DDE. Significant positive associations were present for inhibin B and free testosterone, and inverse associations for sperm volume and progressive sperm (43,48). No associations were found for sperm chromatin integrity, apoptotic markers, epididymal and accessory sex gland function, sperm DNA fragmentation, other reproductive hormones, sperm Y:X ratio, or fertility (43–49).

Unspecified persistent organic pollutants, as evaluated by effects on oestrogen, androgen, or aryl hydrocarbon receptors, were inversely associated with DNA fragmentation index, DNA damage and the anti-apoptotic marker, Bcl-xL (50,51). No associations were found for DNA stainability, semen quality, or the apoptotic marker, Fas (50–52).

Additional studies examined the effects of mercury on semen quality and reproductive hormones (53) and perfluorinated compounds on sperm Y:X ratio (54). Mercury was positively associated with inhibin B but not with other semen characteristics or reproductive hormones (53). Perfluorooctanesulfonate (PFOS) was associated with lower sperm Y:X ratio, though no association was present for perfluorooctanoic acid (PFOA) (54).

Obstetrics and gynaecology
Table III provides details of studies that examined environmental contaminants and effects on obstetrical or gynaecological outcomes. A total of 9 studies, with sample sizes ranging from 22 to 572, were found (55–63). Several inverse associations were observed between contaminants and birth outcomes. PCBs, organochlorine pesticides and mercury were associated with shorter duration of pregnancy and foetal growth (55,60,63). In addition, PCB-153 and p,p′-DDE were associated with lower birth weight and shorter gestational age, but not with risk of preterm birth, in women with live singleton deliveries (56).

Thyroid hormone levels in relation to maternal, cord, or infant levels of PCBs and organochlorine pesticides were evaluated in one study (57). Maternal PCB hydroxylated metabolites, PCB-153, and PCP and cord PCB-153 were associated with thyroid hormones. However, no associations were found with infant contaminant levels.

Menstrual cycle characteristics of women presenting for antenatal care at hospitals were examined by Toft et al. (58). PCB-153 and p,p′-DDE were associated with fewer long menstrual cycles. No association was found between PCB-153 or p,p′-DDE with average cycle length, irregular cycles, or short cycles.

Two small studies (n = 35 and n = 22) measured placental CYP1A1 activity (61,62). One study reported no association with PCBs (61), whereas the other study found increased CYP1A1 activity with higher exposures to PCB-153/PCB-118 and organochlorine pesticides, depending on smoking status (62).

An AMAP report of persistent toxic substances in indigenous populations of the Russian North is available (3). This report was not formally included in this review as it was not in the published literature domain, but results from the report are summarized here. Premature births were associated with blood lead levels > 3.0 μg/L, cadmium > 1.0 μg/L and Aroclor 1,260 > 5.0 μg/L. Reduced birth weight was associated with cadmium and Aroclor at the same thresholds. In addition, women with stillbirths or births with serious structural malformations had PCB, dichlorodiphenyltrichloroethane (DDT) and
| Study       | Contaminant | Outcome                          | Population                                                                 | Results*                                                                 |
|------------|-------------|----------------------------------|-----------------------------------------------------------------------------|--------------------------------------------------------------------------|
| Mocevic (53) | Hg          | Semen quality and reproduc. hormones | Male partners of pregnant women (n = 194)                                   | Inhibin B: Positive association (β = 0.074, 95% CI: 0.021–0.126) No association with other semen characteristics or reproductive hormones |
| Kvist (54)  | PFOA and PFOS | Sperm Y:X ratio                  | Male partners of pregnant women (n = 201) (participation rate: 78.5%)       | PFOS: Inverse association (i.e. lower Y:X ratio) (β = −0.002, 95% CI: −0.004–0.000) PFOA: No association |
| Krüger (37) | PCBs and OCPs | ER, AR and AhR function          | Men and women (n = 247) (participation rate: 41% of all Greenlandic AMAP population and 74% for XAR and XAR$_{comp}$ outcomes) | ΣPCBs: ER transactivity (males): Inverse association (β = −0.36 and −0.24 for XER and XER$_{comp}$ respectively) AhR transactivity (males): No association AhR transactivity (females): Inverse association (β = −0.61) ΣOCPs ER transactivity (males): Inverse association (β = −0.34 for XER) ER transactivity (females): Inverse association (β = −0.36 for XER$_{comp}$) AhR transactivity (males): Inverse association (β = −0.29) AhR transactivity (females): Inverse association (β = −0.55) AR transactivity: No association |
| Krüger (38) | PCBs and OCPs | ER and AR transactivity          | Men and women (n = 240) (participation rate: 82% for XAR/XER outcome)      | ΣPCBs: ER transactivity (males and females): No association upon adjustment AR transactivity (males): Inverse association (β = −0.42) AR transactivity (females): No association ΣOCPs ER transactivity (males): No association ER transactivity (females): Inverse association when adjusted for age (β = −0.24) AR transactivity (males): Inverse association (β = −0.36) AR transactivity (females): No association |
| Bonde (43)  | PCBs and p,p'-DDE | Fertility and markers of male reproductive function | Pregnant women and their spouses (n = 598) (participation rate: 90%) | PCB-153: LH: Positive association (β = 0.07, 95% CI: 0.02–0.12) Sperm volume: Inverse association (β = −0.11, 95% CI: −0.2 to −0.04) Progressive sperm: Inverse association (β = −4, 95% CI: −6 to −1) Sperm counts: Low counts in subgroup of men with short androgen receptor CAG repeat length Neutral α-glucosidase activity in seminal plasma: Inverse association (β = −0.1, 95% CI: −0.2 to −0.0) No association with other measures (e.g. time to conceive, apoptotic markers, sperm chromatin integrity) |
| Study    | Contaminant          | Outcome                          | Population                  | Results*                                    |
|----------|----------------------|----------------------------------|-----------------------------|--------------------------------------------|
| Krüger (50) | POPs (evaluated as effects on ER, AR and AhR) | Sperm chromatin integrity | Male spouses of pregnant women (n = 53) | DNA fragmentation index: Inverse association with ER and AhR activities |
| Long (39) | PCBs and OCPs | AhR transactivity | Men and women 18–77 years of age (n = 357) | ΣPCBs: No association (males or females) with AhR-TEQ |
|          |                      |                                  |                             | Inverse association with AhRcomp in males and females combined (β = −0.18) | ΣOCPs: No association in males; No association in females |
|          |                      |                                  |                             | Inverse association with AhR-TEQ (β = −0.31) in males; No association in females | Inverse association with AhRcomp in males and females combined (β = −0.21) |
|          |                      |                                  |                             | Inverse association with AhRcomp in males and females combined (β = −0.18) |
| Krüger (40) | PCBs and p,p′-DDE | Serum xenoandrogenic activity | Male spouses of pregnant women (n = 37) | PCB-153: No association |
| Toft (52)  | POPs (evaluated as effects on ER, AR and AhR) | Semen quality | Male spouses of pregnant women (n = 54) | No association specifically in Inuit. When data combined across all 4 populations (Warsaw, Greenland, Kharkiv, Sweden), ER activity associated with increase in sperm concentration and motility. |
| Long (51)  | POPs (evaluated as effects on ER, AR and AhR) | Sperm DNA damage and Sperm apoptotic markers | Male spouses of pregnant women (n = 54) | DNA damage: Inverse association with ER and AhR Bcl-xL marker: Inverse association with AR (Spearman’s correlation = −0.46) No association with the sperm apoptotic marker, Fas |
| Long (41)  | PCBs and p,p′-DDE | AhR activity | Males (n = 75) | PCB-153: No association p,p′-DDE: No association |
| Stronati (45) | PCBs and p,p′-DDE | Sperm DNA fragmentation and sperm apoptotic markers | Male spouses of pregnant women (n = 200) (participation rate: 79%) | PCB-153: No association p,p′-DDE: No association |
Table II (Continued)

| Study                  | Contaminant             | Outcome                           | Population                        | Results*                                                                                     |
|------------------------|-------------------------|-----------------------------------|-----------------------------------|-----------------------------------------------------------------------------------------------|
| Elzanaty (47)          | PCBs and p,p-′-DDE      | Epidydymal function and Accessory sex gland function | Male spouses of pregnant women (n = 163) | PCB-153<br>• Epidydymal marker (neutral-α glucosidase): Inverse association (β = −0.2, 95% CI: −0.3 to −0.04)<br>• No association with PSA, zinc, or fructose<br>p,p-′-DDE: No association |
| Giwercman (48)         | PCBs and p,p-′-DDE      | Reproductive hormone levels       | Male spouses of pregnant women (n = 258) | PCB-153<br>• LH: Positive association for highest exposure group compared with lowest exposure group (MD = 1.4 IU/L, 95% CI: 1.1–1.7 IU/L)<br>• No association with other reproductive hormones<br>p,p-′-DDE<br>• Free testosterone: Positive association (β = 0.011, 95% CI: 0.004–0.024)<br>• Inhibin B: Positive association for highest exposure group compared with lowest exposure group (MD = 35 ng/L, 95% CI: 1.5–69 ng/L)<br>• No association with other reproductive hormones |
| Bonefeld-Jorgensen (42)| PCBs and p,p-′-DDE      | Serum xenoestrogenic activity     | Male spouses of pregnant women (n = 72) | PCB-153: No association<br>p,p-′-DDE: Inverse association (Spearman’s correlation = −0.29 for XER) |
| Tiido (49)             | PCBs and p,p-′-DDE      | Sperm Y:X ratio                   | Male spouses of pregnant women (n = 157) | PCB-153: No association<br>p,p-′-DDE: No association |
| Toft (44)              | PCBs and p,p-′-DDE      | Fertility                         | Pregnant women (n = 598) and their spouses (n = 201) | PCB-153: No association<br>p,p-′-DDE: No association |
| Spanò (46)             | PCBs and p,p-′-DDE      | Sperm chromatin integrity         | Male spouses of pregnant women (n = 193) | PCB-153: No association<br>p,p-′-DDE: No association |

AhR = aryl hydrocarbon receptor; AMAP = Arctic Monitoring Assessment Programme; AR = androgen receptor; CI = confidence interval; DDE = dichlorodiphenyldichloroethylene; DNA = deoxyribonucleic acid; ER = oestrogen receptor; Hg = mercury; IU = international unit; LH = luteinizing hormone; MD = mean difference; OCPs = organochlorine pesticides; PCBs = polychlorinated biphenyls; PFOA = perfluorooctanoic acid; PFOS = perfluorooctanesulfonate; POPs = persistent organic pollutants; PSA = prostate specific antigen.  
*Adjusted estimates are presented where available. Presented estimates are statistically significant at p ≤ 0.05 level.
### Table III. Studies of obstetrics and gynaecology

| Study          | Contaminant          | Outcome                          | Population                                      | Results*                                                                 |
|----------------|----------------------|----------------------------------|------------------------------------------------|--------------------------------------------------------------------------|
| [55] Dallaire  | PCBs, HCB and Hg     | Foetal Growth and pregnancy duration | Pregnant women (n = 248) (participation rate: 59%) | Cord PCB-153, HCB and Hg                                                |
|                |                      |                                  |                                                | - Duration of pregnancy: Inverse association (β = −0.17 to −0.20)         |
|                |                      |                                  |                                                | - Fatal growth (mediated through shorter gestation period): Inverse association for length (β = −0.16 to −0.18 for PCB-153 and HCB respectively) |
| [56] Wojtyniak| PCBs and p,p'-DDE    | Birth weight, gestational age and preterm birth | Women with singleton live births (n = 572) (participation rate: 86%) | PCB-153                                                                  |
|                |                      |                                  |                                                | - Birth weight: Inverse association (β = −59.2, 95% CI: −100.6 to −17.8) |
|                |                      |                                  |                                                | - Gestational age: Inverse association (β = −0.2, 95% CI: −0.4 to 0.0)   |
|                |                      |                                  |                                                | p,p'-DDE                                                                  |
|                |                      |                                  |                                                | - Birth weight: Inverse association (β = −39.4, 95% CI: −79.0 to −0.2)   |
|                |                      |                                  |                                                | - Gestational age: Inverse association (β = −0.2, 95% CI: −0.4 to 0.0)   |
|                |                      |                                  |                                                | No association with preterm birth                                        |
| [57] Dallaire  | PCBs, HCB and PCP    | Thyroid hormone levels           | Pregnant women (n = 107) and infants up to 7 months of age (n = 130) | Thyroid hormone levels in women at delivery:                               |
|                |                      |                                  |                                                | Maternal PCB hydroxylated metabolites                                   |
|                |                      |                                  |                                                | - T₃: Positive association (β = 0.57)                                    |
|                |                      |                                  |                                                | - No association with other thyroid hormones                              |
|                |                      |                                  |                                                | Maternal PCB-153, HCB and PCP: No association                                |
|                |                      |                                  |                                                | Thyroid hormone levels in umbilical cord:                                  |
|                |                      |                                  |                                                | Maternal and cord PCB-153                                                |
|                |                      |                                  |                                                | - TBG: Inverse association (β = −0.25 for maternal PCB-153 and −0.26 for cord PCB-153) |
|                |                      |                                  |                                                | - No association with other thyroid hormones                              |
|                |                      |                                  |                                                | Maternal PCP                                                              |
|                |                      |                                  |                                                | - T₄: Inverse association (β = −0.59)                                     |
|                |                      |                                  |                                                | - No association with other thyroid hormones                              |
|                |                      |                                  |                                                | Infant PCB-153 or HCB: No association                                      |
| [58] Toft      | PCBs and p,p'-DDE    | Menstrual cycle                  | Pregnant women presenting for antenatal care at local hospitals (n = 454) (participation rate: 90%) | PCB-153                                                                  |
|                |                      |                                  |                                                | - Long menstrual cycles: Inverse association (OR = 0.7, 95% CI: 0.5 to 0.96) |
|                |                      |                                  |                                                | - No association with average cycle length, irregular cycles, or short cycles p,p'-DDE |
|                |                      |                                  |                                                | - Long menstrual cycles: Inverse association (OR = 0.7, 95% CI: 0.5 to 0.99) |
|                |                      |                                  |                                                | - No association with average cycle length, irregular cycles, or short cycles |
| [59] Lucas     | PCBs and Hg          | Birth weight and gestational age  | Pregnant women (n = 491) (participation rate: 30% for gestational age outcome) | Cord PCB-153                                                             |
|                |                      |                                  |                                                | - Birth weight: Positive association in unadjusted analysis              |
|                |                      |                                  |                                                | Hg: No association                                                       |
| Study | Contaminant | Outcome | Population | Results* |
|-------|-------------|---------|------------|----------|
| Muckle (60) (Abstract only) | PCBs, OCPs and Hg | Developmental effects | Not provided | OCs  
• Physical growth at birth: Inverse association (estimate not provided)  
• Duration of pregnancy: Inverse association (estimate not provided)  
Hg: No information provided |
| Pereg (61) | PCBs | Placental CYP1A1 activity | Pregnant women admitted to hospital upon delivery (n = 35) | No association |
| Lagueux (62) | PCBs and OCPs | Placental CYP1A1 activity and DNA adducts | Women giving birth in regional hospitals (n = 22) | PCB-153, p,p’-DDE, HCB  
• CYP1A1 activity: Positive association in moderate smokers (R² = 0.21, 0.51, 0.38 respectively)  
• CYP1A1 activity: Positive association in heavy smokers (R² = 0.30)  
• Associated with bulky DNA adduct formation in non-smokers and moderate smokers across all cohorts, including non-Inuit  
p,p’-DDE  
• Associated with less bulky DNA adducts across all cohorts, including non-Inuit |
| Foldspang (63) | Hg | Gestational length and birth weight | Mothers with singleton deliveries (n = 376) (participation rate: 45.9% newborns represented from one district) | Birth weight: Inverse association (β = −7.1 for maternal blood mercury and −4.2 for offspring blood mercury)  
No association with gestational length |

CI = confidence interval; DDE = dichlorodiphenyldichloroethylene; DNA = deoxyribonucleic acid; fT₄ = free thyroxine; HCB = hexachlorobenzene; Hg = mercury; OCs = organochlorines; OCPs = organochlorine pesticides; OR = odds ratio; PCBs = polychlorinated biphenyls; PCP = pentachlorophenol; T₃ = triiodothyronine; TBG = thyroxine-binding globulin.

*Adjusted estimates are presented where available. Presented estimates are statistically significant at p ≤ 0.05 level.
mercury levels 1.7–2.0 times higher compared with women with no adverse birth outcomes. An examination of dose-response relationship found that sum of PCBs in maternal serum >2.0 μg/L was associated with birth weight and gestational age and >4.0 μg/L with fatal pregnancy outcomes. In addition, the ArcRisk project, which examined environmental contaminants in Eastern Arctic regions, conducted meta-analyses of the association between PCBs and sex ratio and birth weight (4). No association was found between PCBs and sex ratio, but maternal PCB concentration was associated with low birth weight.

Cardiology
Surrogate outcomes of cardiovascular disease, most commonly blood pressure, have been assessed in several studies (64–69) (Table IV). Other outcomes include resting heart rate and pulse pressure, plasma lipids and cardiac autonomic activity (65,68,70). The studies were large, with sample sizes ranging from 230 to 1,861.

Two studies, including the largest one with 1,861 participants, found that mercury was associated with lower diastolic blood pressure (65,66). However, 2 other studies (n = 732 and n = 280) found no association with diastolic blood pressure (67,68). Results were similarly inconclusive for systolic blood pressure (i.e. positive association in 2 studies but no association in others) (65–68). A study of reindeer herders in northernmost Arctic Finland found that hypertensive subjects had higher blood cadmium levels compared with normotensives and that blood cadmium was positively associated with systolic blood pressure when adjusted for age, body mass index, smoking and alcohol consumption (69).

The risk of hypertension (i.e. blood pressure of ≥140/90 mm Hg or taking anti-hypertensive medication) was higher in younger individuals (18–39 years of age) exposed to dioxin-like PCBs (OR = 1.34, 95% CI: 1.03–1.74) or DDT (OR = 1.42, 95% CI: 1.08–1.85) (64). Interestingly, the risk was lower in older individuals (≥40 years) exposed to non-dioxin-like PCBs or Mirex (64).

PFOS was inversely associated with triacylglycerol and ratio of total cholesterol/high density lipoprotein cholesterol (HDL-C) and positively with HDL-C after controlling for n-3 polyunsaturated fatty acids (70). No association was found between PFOS and low density lipoprotein cholesterol (LDL-C) or non-HDL-C.

Endocrinology
In one study of 692 middle-aged men and women in Greenland, PCBs and organochlorine pesticides were not associated with impaired glucose tolerance or diabetes (71) (Table IV). Nor were they associated with the surrogate outcomes of fasting glucose, 2-hour glucose, or fasting insulin. Significant inverse associations were found between PCBs and organochlorine pesticides with 2-hour insulin and between PCBs and the homeostasis model assessment of β-cell function.

Dallaire et al. reported on thyroid hormone levels in relation to PCBs, organochlorine pesticides, PBDEs, PFOS and dioxin-like compounds in 623 men and women 18 years of age or older in Nunavik (72). Significant inverse associations were observed for PCBs, hexachlorobenzene, β-hexachlorocyclohexane and PFOS with total triiodothyronine, thyroxine-binding globulin, free thyroxine and/or thyroid-stimulating hormone. p,p’-DDE and PBDEs, however, were not associated with any measure of thyroid function after adjusting for confounders.

Bone health
Two studies assessed bone strength and bone ultrasound in relation to dioxin-like PCBs or PCBs and organochlorine pesticides, respectively, in peri- and postmenopausal women (73,74) (Table IV). No association was present between bone strength and dioxin-like PCBs (73) or between PCB-153 and bone ultrasound quantitative parameters (74). PCB-156 congener was associated inversely with broadband ultrasound attenuation (indication of bone density and architecture), speed of sound (indication of bone density and elasticity) and stiffness index (indication of rigidity of bone structure).

Oncology
Breast cancer and exposure to PCBs, organochlorine pesticides, perfluorinated compounds and heavy metals were examined in a case–control study in Greenland (n = 31 cases and n = 115 controls matched for age and district) (75) (Table IV). Perfluorinated compounds and the sum of persistent organic pollutants were associated positively with breast cancer (OR = 1.03, 95% CI: 1.00–1.05 and OR = 1.02, 95% CI: 1.01–1.04, respectively). PCB, as a continuous measure, was not associated with breast cancer, but within the highest quartile level, exposure was significantly higher for cases than controls. No association was found with organochlorine pesticides or heavy metals.

DNA hypomethylation, an epigenetic mechanism causing chromosomal instability and alteration of gene expression, was examined in a small study (n = 70) consisting mostly of males aged 19–67 years in Greenland (76). PCBs, p,p’-DDE, DDT, other organochlorine pesticides and the sum of persistent organic pollutants were all significantly associated with DNA hypomethylation based on the Alu assay but not based on the LINE-1 assay. The authors suggest that the different mechanisms and transcription patterns in response to cellular stressors accounts for the significant associations observed in one assay and non-significant associations in the other assay.

Other
The capacities of PCBs and mercury to induce oxidative stress were evaluated in 2 studies of men and women from
### Table IV. Studies of cardiology, endocrinology, bone health, oncology and oxidative stress in adults

| Study       | Contaminant | Outcome                                      | Population | Results*                                                                 |
|-------------|-------------|----------------------------------------------|------------|--------------------------------------------------------------------------|
| Cardiology  |             |                                              |            |                                                                           |
| Valera (64) | PCBs and OCPs | Hypertension (≥ 140/90 mm Hg or taking anti- | Men and women ≥ 18 years of age (n = 1,614) | | |
|             |             | hypertensive medication)                     | (participation rate: 52% from larger population) | | |
|             |             |                                              |            | **ΣDL-PCBs**                                                             | |
|             |             |                                              |            | • Hypertension: Positive association in youngest age category (18–39 years) | |
|             |             |                                              |            | (OR = 1.34, 95% CI: 1.03–1.74) | |
|             |             |                                              |            | **Σnon-DL-PCBs**                                                         | |
|             |             |                                              |            | • Hypertension: Inverse association in oldest age category (≥ 40 years) (OR = 0.81, 95% CI: 0.66–0.99) | |
|             |             |                                              |            | **DDT**                                                                 | |
|             |             |                                              |            | • Hypertension: Positive association in youngest age category (18–39 years) | |
|             |             |                                              |            | (OR = 1.42, 95% CI: 1.08–1.85) | |
|             |             |                                              |            | **Aldrin, α-chlordane, γ-chlordane**                                    | |
|             |             |                                              |            | • Hypertension: Inverse associations in youngest age category (18–39 years) | |
|             |             |                                              |            | (OR = 0.39, 95% CI: 0.20–0.78; OR = 0.38, 95% CI: 0.19–0.75; OR = 0.10, 95% CI: 0.03–0.38 respectively) | |
|             |             |                                              |            | **Mirex**                                                                | |
|             |             |                                              |            | • Hypertension: Inverse association in oldest age category (≥ 40 years) (OR = 0.80, 95% CI: 0.69–0.93) | |
| Valera (65) | Hg          | Blood pressure, resting heart rate and pulse  | Men and women ≥ 18 years of age (n = 313) | Resting heart rate: Positive association | |
|             |             | pressure                                      | (participation rate: 41%)                     | Diastolic blood pressure: Inverse association | |
| Nielsen (66)| Hg          | Blood pressure                                | Men and women 30–69 years of age (n = 1,861) | No association with systolic blood pressure or pulse pressure | |
|             |             |                                              | (participation rate: 67.5%)                    | Diastolic blood pressure: Inverse association in men (β = −0.04) | |
| Valera (67) | Hg          | Blood pressure                                | Men and women ≥ 18 years of age (n = 732) | Systolic blood pressure: Positive association (β = 2.14, 95% CI: 0.94–3.33) | |
|             |             |                                              | (participation rate: 55%)                      | Diastolic blood pressure: No association | |
| Château-Degat(70)| PFOS | Plasma lipids                                  | Men and women 18–74 years of age (n = 723) | Triacylglycerol: Inverse association in women (β = −0.0014) | |
|             |             |                                              | (participation rate: 68%)                      | HDL-C: Positive association (β = 0.0042 and 0.0016 for women and men respectively) | |
|             |             |                                              |            | Ratio TC/HDL-C: Inverse association (β = −0.0035) | |
|             |             |                                              |            | No association with LDL-C or non-HDL-C | |
| Valera (68) | Hg          | Blood pressure and cardiac autonomic activity | Men and women ≥ 40 years of age (n = 280) | SDANN: Inverse association (β = −0.086, 95% CI: −0.16 to −0.01) | |
|             |             |                                              | (participation rate: 59%)                      | Systolic blood pressure: Positive association (β = 4.77, 95% CI: 1.12–8.42) | |
|             |             |                                              |            | Pulse pressure: Positive association (β = 3.40, 95% CI: 1.11–5.69) | |
|             |             |                                              |            | No association with diastolic blood pressure or other measures of cardiac autonomic activity | |
| Luoma (69)  | Cd          | Blood pressure and arterial hypertensive      | Reindeer herders 20–82 years of age in Arctic | Systolic blood pressure: Positive association | |
|             |             | disease                                       | Finland (n = 230)                              | Diastolic blood pressure: No association | |
|             |             |                                              | (participation rate: 14%)                      |                           |
| Study | Contaminant | Outcome | Population | Results* |
|-------|-------------|---------|------------|----------|
| **Endocrinology** | | | | |
| Jørgensen (71) | PCBs and OCPs | Glucose intolerance | Men and women (mean age 49 years) (n = 692) (participation rate: 67%) | PCBs and OCPs 2-hour insulin: Inverse association DL-PCBs and non-DL-PCBs HOMA-B: Inverse association. No association with mean fasting glucose, mean 2-hour glucose, or mean fasting insulin. No association with IGT or diabetes. |
| Dallaire (72) | PCBs, OCPs, PBDEs, PFOS and dioxin-like compounds | Thyroid function | Men and women ≥ 18 years of age (n = 623) (participation rate: 50%) | PCBs T₃: Inverse association (β = −0.020) (inverse association also for PCB metabolites) TBG: Inverse association (β = −0.037) (inverse association also for PCB metabolites) HCB T₃: Inverse association (β = −0.030) fT₄: Inverse association (β = −0.017) TBG: Inverse association (β = −0.054) β-HCH T₃: Inverse association (β = −0.028) TBG: Inverse association (β = −0.051) PFOS T₃: Inverse association (β = −0.017) fT₄: Positive association (β = 0.014) TBG: Inverse association (β = −0.034) TSH: Inverse association (β = −0.102) No associations with p,p'-DDE or PBDEs after full adjustment for confounders |
| **Bone health** | | | | |
| Paunescu (73) | DL-PCBs (evaluated as effects on AhR) | Bone strength | Women 35–72 years of age (n = 194) | No association |
| Côté (74) | PCBs and OCPs | Bone ultrasound | Peri- and post-menopausal women 49–64 years of age (n = 153) | PCB-156  • Broadband ultrasound attenuation (indication of bone density and architecture): Inverse association (β = −8.12)  • Speed of sound (indication of bone density and elasticity): Inverse association (β = −22.68)  • Stiffness index (indication of rigidity of bone structure): Inverse association (β = −11.95) PCB-153: No association |
| **Oncology** | | | | |
| Bonefeld-Jørgensen (75) | PCBs, OCPs, PFCs and heavy metals | Breast cancer | Cases (n = 31) and controls (n = 115) | PCBs  • Highest quartile of exposure significantly higher for cases than controls. Otherwise no association. |
| Study          | Contaminant   | Outcome                                                                 | Population                                                                 | Results*                                                                                                    |
|----------------|---------------|--------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------|
| Rusiecki (76)  | PCBs and OCPs | DNA methylation (Alu and LINE-1 assays)                                  | Mostly males 19–67 years of age (n = 70)                                                                                       | PFCs: Positive association with breast cancer (OR = 1.03, 95% CI: 1.001–1.07 for PFOS and 1.03, 95% CI: 1.00–1.05 for Σperfluorosulfonated acids) |
|                |               |                                                                          |                                                                             | ΣPOPs: Positive association (OR = 1.02, 95% CI: 1.01–1.04)                                                                      |
|                |               |                                                                          |                                                                             | OCPs: No association                                                                                               |
|                |               |                                                                          |                                                                             | Heavy metals: No association                                                                                           |
|                |               |                                                                          |                                                                             | ΣPCBs: Inverse association on Alu assay (β = −0.56) (i.e. DNA hypomethylation) p.p’-DDE, DDT, other pesticides | |
|                |               |                                                                          |                                                                             | Inverse associations on Alu assay (β = −0.26 to −0.75)                                                                     |
|                |               |                                                                          |                                                                             | ΣPOPs: Inverse association on Alu assay (β = −0.48)                                                                       |
|                |               |                                                                          |                                                                             | No association on LINE-1 assays                                                                                         |
| Other          | PCBs and Hg   | Oxidative stress (redox status of CoQ10 and vitamin E)                   | Men and women (majority women) (n = 99)                                                                                       | ΣPCBs: Total tocopherols: Positive association (β = 2.68)                                                               |
|                |               |                                                                          |                                                                             | α-Tocopherol: Positive association (β = 4.12)                                                                                |
|                |               |                                                                          |                                                                             | Ratio α-tocopheryl quinone/α-tocopherol: Inverse association (β = −0.41)                                                      |
|                |               |                                                                          |                                                                             | Overall, no evidence of oxidative stress                                                                                 |
|                |               |                                                                          |                                                                             | Hg: α-Tocopheryl quinone: Inverse association (β = −0.30)                                                                  |
|                |               |                                                                          |                                                                             | Overall, no evidence of oxidative stress                                                                                 |
|                |               |                                                                          |                                                                             | No association with ubiquinol-10 or ubiquinone-10 and PCBs or Hg                                                            |
| Bélanger (77)  | PCBs and Hg   | Oxidative stress (plasma oxidized LDL-C, homocysteine, glutathione peroxidase, glutathione reductase and glutathione) | Men and women (majority women) (n = 99)                                                                                       | PCBs: Oxidized LDL-C: Positive association (β = 0.11)                                                                    |
|                |               |                                                                          |                                                                             | Hg: No association                                                                                                 |

AhR = aryl hydrocarbon receptor; Cd = cadmium; CI = confidence interval; DDE = dichlorodiphenyldichloroethylene; DDT = dichlorodiphenyltrichloroethane; DL-PCBs = dioxin-like polychlorinated biphenyls; DNA = deoxyribonucleic acid; fT4 = free thyroxine; HCB = hexachlorobenzene; HCH = hexachlorocyclohexane; HDL-C = high density lipoprotein cholesterol; Hg = mercury; HOMA-B = homeostasis model assessment of beta cell function; IGT = impaired glucose tolerance; LDL-C = low density lipoprotein cholesterol; OCPs = organochlorine pesticides; OR = odds ratio; PBDEs = polybrominated diphenyl ethers; PCBs = polychlorinated biphenyls; PFCs = perfluorinated compounds; PFOs = perfluorooctanesulfonate; POPs = persistent organic pollutants; SDANN = standard deviation of the average RR intervals calculated over 5 minute periods; T3 = triiodothyronine; TBG = thyroxine-binding globulin; TC = total cholesterol; TSH = thyroid-stimulating hormone.

*Adjusted estimates are presented where available. Presented estimates are statistically significant at p ≤ 0.05 level.
Nunavik (n = 99 each) (77,78) (Table IV). One study examined redox status of coenzyme Q10 and vitamin E (tocopherol) (78) and the other examined oxidation of LDL-C, homocysteine, glutathione peroxidase, glutathione reductase and glutathione (77). Based on tocopherol and coenzyme Q10 redox status, neither PCBs nor mercury increased oxidation, although the elevated ratio of ubiquinone-10 to coenzyme Q10_total indicated that the population was experiencing oxidative stress (78). Similarly, in the second study, mercury did not increase oxidation (77). However, PCBs were associated with higher levels of oxidized LDL-C, suggesting that PCBs participate in oxidative stress (77).

**Discussion**

A broad range of epidemiological studies have evaluated the possible human health effects of environmental contaminants. However, there are only 60 published studies conducted in Arctic indigenous populations. Several of these studies found association of contaminants with children's immune status, behaviour, neurological function, heart rate variability and thyroid function. In addition, in adults several associations between contaminants and adverse outcomes have been observed, including those on reproductive outcomes, foetal growth and duration of pregnancy, blood pressure and hypertension, thyroid hormones, quantitative measures on bone ultrasound, breast cancer, DNA hypomethylation and oxidative stress. Most of these studies attempted to adjust for several relevant confounders.

Unfortunately, we are still far from being able to make any conclusive statements about the health effects of most environmental contaminants. First, the evidence is largely interspersed with studies showing significant associations and studies showing no associations (i.e. statistical significance not reached). The latter may be due to studies with small sample sizes that are underpowered to detect significant differences. Also, of the studies with larger sample sizes (200+), participation rates ranged from 14 to 95%, with average of 65%, which suggests that there may be issues with the representativeness of study samples. Second, for many contaminant–outcome pairs, we have only 1 or 2 studies contributing data. Conclusions based on observational epidemiological evidence should be based on an accumulation of good quality data that points towards a common direction. Good quality data will come from well-designed observational studies that have representative samples, pre-defined outcomes and subgroup analyses, power calculations and measurement of confounders. Admittedly, epidemiological studies are difficult to conduct in Arctic regions that have small populations and limited accessibility (79). One way to overcome the problems of small sample sizes in individual studies and few studies in Arctic populations is to conduct a meta-analytical synthesis of the literature base on priority contaminants and health outcomes. A necessary component in synthesizing the literature will be to assess the quality of the individual studies. In particular, one issue that came to light during this review is the large number of statistical analyses (i.e. based on different contaminant congeners and subgroups) that were carried out by some studies. Such analyses may result in spuriously significant associations by chance alone. Therefore, it will be important to determine if such subgroup analyses were pre-specified and if they make biological sense.

There are several gaps in the literature, which require future research attention. Published epidemiological studies linking environmental contaminants to health outcomes have been primarily conducted in only 2 regions – Nunavik and Greenland. Additionally, data on obstetrical outcomes are available in indigenous populations of Russian and European North in AMAP reports. It would be informative if data can be accumulated and published from other Arctic populations in Canada (e.g. Inuvialuit Settlement Region, Nunavut, Nunasiavut), Alaska, Russian North and European North. Secondly, while the data in paediatrics and reproductive health are quite extensive, studies available for other areas are notably sparse. For instance, few studies are available on chronic diseases such as cardiovascular disease and diabetes, which make up a large burden of health problems faced by Arctic populations. In addition, only surrogate outcome of cardiovascular disease has been measured. Future studies, therefore, should focus on clinical endpoints as well, such as incidence of heart disease or myocardial infarction. In these respects, analyses of the Adult Inuit Health Survey, which was a cross-sectional survey of about 2,600 Inuit adults from Inuvialuit Settlement Region, Nunavut Territory and Nunasiavut, and which collected information on heart disease and diabetes, will be useful (80). Lastly, as shown in Figure 3, only a few studies (4 in total) have evaluated PBDEs or perfluorinated compounds. Both have been classified as emerging contaminants in the Arctic (5) and, therefore, more studies on these contaminants and effects on human health are needed.

An important next step is to translate the findings of these and future research studies into meaningful communication messages to policy makers and the populations directly affected by contaminant exposures. Such messages must be evidence-based but also sensitive to the traditions and needs of Arctic regions. Traditional foods are integral to the Arctic peoples’ cultures, through which social cohesion is maintained (5). In addition, traditional foods are a source of nutrients, such as essential fatty acids, which are not adequately obtained from market foods (5). Therefore, messages must incorporate a holistic approach to properly balance the risks of environmental contaminants in traditional foods with their benefits. Such communication is likely to be successful through...
multistakeholder engagement that includes dialogue from the perspectives of science, policy and communities.

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