Chemicals of Concern in Ontario and The Great Lakes Basin –
Update 2011
Emerging Issues

Submitted to Health Canada by

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INTRODUCTION

Despite progress in reducing pollutants in the past decade, concerns regarding the level of releases and human health outcomes associated with various compounds remain. This report adds to the previous 2007 one (http://mcmaster.ca/mieh/documents/publications/COC_Report_Update.pdf). It brings our reference search up to March 2011, covering the period from early 2007 to then. In this interim, the 2009 State of the Lakes report highlights declines in levels of contamination in birds and fish but a continuing undetermined relationship between lake status and human health. Since our last update in 2007, OECD (2008) brought out in environmental outlook and the Government of Canada has rigorously pursued its Chemicals Management Plan, carrying out risk assessments on some 200 chemical substances in use or production in Canada (http://www.chemicalsubstanceschimiques.gc.ca/index-eng.php). ATSDR (2008) has released its report on chemical releases in the Great Lakes Basin. Pollution Watch (2010) also published its second partners in pollution report. In Ontario, the government passed a toxic reduction act in 2009, using National Pollution Registry Inventory (NPRI) as a basis of classifying toxic substances and part of which included the cosmetic pesticide ban. The IJC (2010) also commissioned work on environmental exposures in the Great Lakes.

OECD (2008) point to the diversity of chemicals with many uses, ranging from large volume commodity chemicals used as building blocks, to more specialised uses (e.g., in coatings, electronics, additives, etc.); and from life science products (e.g., pharmaceuticals, pesticides) to consumer care products. While these chemicals can improve the lives of people, their production and use can also have a negative impact on human health and the environment. The releases of certain substances can cause serious damage to human health and the environment, as has been seen in the past from harmful levels of exposure to PCBs, DDT, and PBBs. Concern has been raised about the link between reproductive and developmental effects and endocrine disrupting substances in wildlife (e.g., some alkylphenols used as raw materials in the production of a variety of industrial products, such as surfactants, detergents, phenolic resins, polymer additives and lubricants, can cause endocrine disruption in fish by interfering with oestrogen). This report also points to the increased international and national regulatory and monitoring regimes that are being developed with declarations on chemical management.

The Government of Canada has reviewed some 23,000 substances to categorize them into whether they required further investigation if they presented a potential risk to the environment or human health. Some 300 were seen as possibly important because of their effects on human health and have been reviewed in 12 batches between 2006 and 2010. This monitoring and evidence gathering is important to maintain the reduction of chemical releases. Emissions of hazardous substances from chemical plants have generally been steadily decreasing, as have overall releases of chlorofluorocarbons (CFCs). According to the Commission for Environmental Cooperation, total releases and transfers of the 152 chemicals that are common to the U.S. and Canada and monitored by both countries, dropped 18% between 1995 and 2002 (CEC, 2005).

Furthermore, ATSDR (2008) report on the U.S. areas of concern (AOC). The report concludes that as a result of both past and ongoing releases, environmental pollution in the Great Lakes region is widespread. Of 146 hazardous waste sites located in AOC counties and evaluated by ATSDR, many have been remediated; but others are still undergoing long-term remediation. In addition, recent data
from EPA databases demonstrate ongoing chemical releases in the region. Throughout the region, fish tissue monitoring detects contaminant levels at or above levels thought to pose a risk to human health as determined by state and federal regulatory agencies. These monitoring efforts have led to the issuance of advisories to limit fish or wildlife consumption in all but one of the 26 AOCs—Presque Isle Bay, Pennsylvania. Fish advisories that result from chemical releases into an AOC are in some cases specific to locations within that AOC, and in other instances are regional. The report cannot reflect the totality of chemical pollution in the region. Many sources of contamination exist that are not ATSDR-evaluated sites. TRI data did not reflect the totality of toxic releases: reporting exemptions included small firms, firms from certain industry sectors, and other categories of emitters. The NPDES data did not include information on nonpoint-source water pollutants. Thus, available data even taken together do not include exposures from pesticide applications, from mobile sources, or from indoor sources. Hence the data provide only a partial picture of contaminants in the environment. But the available information on environmental pollution provides little insight on the exposure of people to pollutants. TRI data on chemicals used and emitted, and NPDES data on chemicals discharged into water, do not indicate whether these chemicals reach people and enter their bodies. ATSDR assessments of hazardous waste sites do, however, include analysis of exposure pathways, and, when available, include data on how much exposure actually occurs. Current data do not allow us to draw firm conclusions about relationships between critical pollutants in the Great Lakes region and potential health effects.

Data that are routinely collected (such as information on cancer and birth defects) are not well matched to exposure data in time or by location and therefore cannot help to assess whether the identified environmental exposures have adverse health consequences. Pollution Watch (2010) reports that overall, releases and transfers in the Great Lakes-St. Lawrence River basin from reporting NPRI and TRI facilities decreased in the past five years (2003-2007). However, on- and off-site land disposal increased. Air releases decreased basin wide by 18 million kg, or 19% from 2003 to 2007. Air releases decreased by 13 million kg, or 30%, for NPRI (Canadian) facilities in the Great Lakes-St. Lawrence River basin, driven by large reductions in a few facilities. Four facilities reported reductions of over one million kg and accounted for almost half (6.4 million kg) of the reductions Air releases from TRI (U.S.) facilities also showed a decrease, of 4 million kg or 9%. However, for TRI facilities, there were increases in air releases over the past five years in the Lake Erie basin (including one electric power plant with increases over 3 million kg, primarily of hydrochloric acid), along the St. Lawrence River and in the Lake Superior basin.

Air releases of carcinogens also decreased basin wide, by 36%, for both NPRI and TRI facilities. Facilities no longer reporting in 2007 accounted for about half of the decrease (53% in NPRI and 48% in TRI). NPRI facilities with the largest decrease in air releases of carcinogens included dichloromethane releases in 2003 from three manufacturers of plastic foam products who had ceased to report to NPRI by 2007. The TRI facility with the largest decrease (a chemical manufacturer of photographic supplies) also reported a large decrease in dichloromethane. Air releases of reproductive and developmental toxins decreased basin-wide by 34%, with NPRI showing a decrease of 42% and TRI a decrease of 18%. Toluene accounted for more than three quarters of air releases of reproductive/developmental toxins in NPRI and more than two-thirds in TRI. Both NPRI and TRI showed a decrease of more than 15% in air releases of toluene from 2003 to 2007.
Water releases from NPRI and TRI facilities decreased basin wide by 25% in the five years from 2003 to 2007. Water releases from matched NPRI facilities decreased by 37% and TRI facilities decreased by 19%. Among the four facilities with the largest decreases, three no longer reported in 2007. Water releases decreased in all of the basins except for Lake Superior where water releases increased by 64%. Two NPRI pulp and paper mills in the Lake Superior basin each reported over 26,000 kg of water releases of manganese (and its compounds) for 2007 and had not reported on this chemical for 2003. This may reflect changes in reporting guidance. Water releases of known carcinogens also decreased basin wide (by 9%) in the past five years, with TRI facilities reporting a decrease of 32%. However, matched NPRI facilities showed an increase of 7%. Three NPRI pulp and paper mills reported increases of over 1,300 kg of water releases of formaldehyde from 2003 to 2007.

Both on-site land disposal and releases and off-site releases (transfers to disposal, mainly to landfills) increased overall in the Great Lakes-St. Lawrence River basin. However, for NPRI facilities, while on-site land releases increased (by 69%), off-site transfers to disposal decreased (by 26%). For known carcinogens, land disposal and releases both on- and off-site increased for NPRI facilities. Two hazardous waste management facilities accounted for more than three quarters (77%) of the increase. One (Stablex in Blainville, Quebec) increased disposal of lead (and its compounds) and the other (Newalta Industrial Services in Stoney Creek, Ontario) had an increase in disposal of asbestos. For TRI facilities, however, on-site land releases decreased (by 2%) and off-site transfers to disposal increased (by 28%). For known carcinogens, on-site land disposal and releases also decreased although off-site releases increased.

Underground injection decreased by 27% from 2003 to 2007; underground injection is mainly found at five TRI facilities in the Lake Erie and Lake Michigan basins. The decrease was due to reductions at two TRI chemical manufacturers; Ineos USA LLC in Lima, Ohio, reduced its underground injection by 48% and Pfizer Inc. in Holland, Michigan, reduced by 91%. The other facilities reporting underground injection for 2007 reported increases from 2003 to 2007.

Overall, in its report, Pollution Watch (2010) shows that there are 204 pollutants and 3,960 facilities in the data sets for the Great Lakes-St. Lawrence River basin. Some 285 million kg of pollutants were released and transferred (excluding recycling) from NPRI and TRI facilities in 2007. Approximately 75 million kg of pollutants were released into the air from NPRI and TRI facilities. About 5 million kg of pollutants under Canada’s NPRI and U.S. TRI were released to water. However, this is a large underestimation of the pollutants released to water because wastewater treatment plants do not report to TRI and, therefore, are not included in the dataset. About 10 million kg of chemicals were also injected underground, mainly by a handful of U.S. facilities along Lake Erie. About 50 million kg of chemicals were land filled on site and even more (almost 70 million kg) were transferred to other sites for disposal. About 250 million kg of reported pollutants were recycled. The Lake Erie basin had the largest number of facilities and half of the total reported releases in the Great Lakes-St. Lawrence River basin. It also had the largest amounts of air releases, land releases and underground injection of all the Lakes. This is concerning as Lake Erie is the smallest and shallowest of all the Lakes. Canadian NPRI facilities emitted more known carcinogens and reproductive developmental toxicants to the air than U.S. TRI facilities. This finding is not due to the different numbers of facilities; NPRI facilities are only one third of the total Great Lakes-St. Lawrence River facilities reporting carcinogens and one-half of facilities reporting reproductive/developmental toxicants. On a per facility basis, Canadian NPRI
facilities emitted to the air, on average, almost three times more known carcinogens and more than twice the reproductive/developmental toxins than U.S. TRI facilities.

From the IJC report, it is apparent that a wide variety of chemicals of emerging concern have been detected in environmental media (i.e., air, water, sediment, biota) from the Great Lakes Basin, although many are present at only trace levels. Although the presence of these contaminants raises concerns in the public and among the scientific community, the findings must be placed in context. Significant scientific interpretation is required to understand the extent to which these chemicals may pose a threat to the ecosystem and to human health. The ability to detect chemicals in environmental media greatly surpasses our ability to understand the implications of such findings. As advances in analytical technologies occur, it is probable that substances previously found to be non-detectable will be detected. However, their presence in environmental media should not be construed to mean that they are necessarily toxic or hazardous. Current-use pesticides are tightly regulated and extensive efforts have been made to analyze for their presence in surface waters from the Great Lakes Basin. The concentrations found in surface waters for many of the pesticides are below current regulatory criteria. However, the concentrations of certain pesticides exceeded current criteria in 6-32% of the samples analyzed. Detectable concentrations of pharmaceutical compounds were present in 34% of the surface water samples. Various prescription and non-prescription drugs were detected, most frequently at locations that were proximate to the point of discharge from wastewater treatment plants or agricultural operations. At present, there are no standards, guidelines, or criteria with which to compare these contaminant concentrations.

Concentrations of alkylphenol ethoxylates and their metabolites have been well studied. All surface water nonylphenol concentrations were below U.S. ambient water quality criteria. However, the concentrations reported for some locations exceeded Canadian guidelines for water or sediment. Only limited data were available for a wide variety of organic wastewater contaminants. Measured concentrations in Great Lakes waters were generally low. Where criteria exist for comparison, the concentrations found were generally below the associated regulatory standards. However, exceedences were noted for some classes of compounds, including phthalates and polycyclic aromatic hydrocarbons. Discharges from wastewater treatment plants were identified as an important source of contaminants to surface waters in the Great Lakes Basin. Combined sewer overflows and agricultural operations were also found to be important contributors to concentrations in surface waters. Concentrations of many of the chemicals were generally the highest in the vicinity of these sources, decline with increasing distance from sources, and were generally low or non-detectable in the open waters of the Great Lakes. The highest environmental concentrations were reported in biota for a number of persistent, bioaccumulative, and toxic compounds (e.g., polybrominated diphenyl ethers, perfluorinated surfactants).

Various stewardship as well as government risk assessment and risk management programs have been implemented over the past years for many of these compounds. Because risk management strategies for some of these contaminants have been implemented only recently, their impact on environmental concentrations, to date, remains unclear. Current evidence suggests that the concentrations of some brominated flame retardants are trending downward, while the concentrations of others appear to be increasing. Regulatory criteria are not available for many of the chemicals of emerging concern that were detected in the Great Lakes Basin. When criteria do exist, it is important to recognize that they were developed based on the best available science at the time.
As the science evolves, regulatory criteria must be reassessed in light of new findings (e.g., consideration of new endpoints and mechanisms of action). Further, there are significant scientific gaps in our ability to interpret environmental monitoring data, including the need for: (a) improving the understanding of the effects of mixtures, (b) information on use of, and the commercial life cycle of chemicals and products that contain them, (c) information on source contributions and exposure pathways, and (d) the need for thoughtful additional regulatory, environmental, and health criteria.

Progress has then been made in reducing many persistent organic pollutants such as the organochlorine compounds in the water and in fish commonly consumed, although this appears to have leveled off in recent years (LaRoe, 1995; USEPA, 2002). Although air releases were larger than water releases, deposition of contaminants in water and soil remain major pathways to human exposure. In The U.S., voluntary pollution reduction has since gained ground (see Bennear, 2007; Innes and Sam, 2008). Concern also remains about several groups of unmonitored chemicals including pharmaceuticals and personal care products (PPCPs) and polybrominated diphenyl ethers (PBDEs). Newly emerging concerns include ethoxylates, phthalates, disinfectant by-products (DBPs), nanotechnology, anti-microbial resistance (a subset of PPCPs), synergistic effects and endocrine disrupting chemicals, and high–volume chemicals such as biodegradable pesticides, given they are persistent, but usually biodegradable, and not all of them are bioaccumulative (IJC, 2000; 2002). There has been more attention paid to prenatal exposure and evidence from biomonitoring has enabled some greater focus on effects and pathways, although reference doses are not available for many substances.

In the following report, we update the 2005 and 2007 Chemicals of Concern in Ontario reports submitted to Health Canada. This revised report also focuses extensively upon (i) the group of substances identified as ‘emerging contaminant issues’, (ii) some new substances and, (iii) emerging outcomes and pathways of concern. We do not repeat the materials discussed in the earlier reports as this version is supplementary to them. We have also used different subheadings within the substances. We recognize that much of the audience reading the report is interested in health outcomes specifically. We, therefore, attach recent ATSDR reports (http://www.atsdr.cdc.gov/substances/ToxOrganSystems.asp) on the impact of chemicals on health and put in Appendix 1 their December 2010 Minimum Risk Level report. We also link this report to the Health Canada materials on environmental impacts on health in “Healthy Living: It’s Your Health” (http://www.hc-sc.gc.ca/hl-vs/iyh-vsv/environ/index2-eng.php). While set out differently from the 2005 and 2007 reports, it uses the backdrop of the agency and departmental commentaries outlined in this introduction.
Figure 1. Facilities Reporting in 2007 to Canada’s National Pollutant Release Inventory and the United States’ Toxic Release Inventory for Air Releases of Toxics in the Great Lakes and St. Lawrence River Basin.

Source: Pollution Watch. 2010, p. 10.
Figure 2. Air Releases of Combined Pollutants in Census Subdivisions in the Great Lakes Basin

Table 1. Total Reported Releases for 2007, by Basin, NPRI and TRI

<table>
<thead>
<tr>
<th>Basin</th>
<th>NPRI (kg)</th>
<th>TRI (kg)</th>
<th>Total (kg)</th>
<th>% of Total (NPRI)</th>
<th>% of Total (TRI)</th>
<th>% of Total (Total)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lake Erie</td>
<td>16,393,329</td>
<td>87,895,455</td>
<td>104,288,784</td>
<td>25</td>
<td>62</td>
<td>50</td>
</tr>
<tr>
<td>Lake Michigan</td>
<td>0</td>
<td>43,928,216</td>
<td>43,928,216</td>
<td>0</td>
<td>31</td>
<td>21</td>
</tr>
<tr>
<td>St. Lawrence River</td>
<td>25,474,031</td>
<td>463,418</td>
<td>25,942,449</td>
<td>38</td>
<td>0</td>
<td>12</td>
</tr>
<tr>
<td>Lake Ontario</td>
<td>18,806,189</td>
<td>5,019,145</td>
<td>23,825,334</td>
<td>28</td>
<td>4</td>
<td>11</td>
</tr>
<tr>
<td>Lake Huron</td>
<td>3,890,057</td>
<td>2,864,256</td>
<td>6,754,313</td>
<td>6</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Lake Superior</td>
<td>1,896,341</td>
<td>2,308,007</td>
<td>4,204,348</td>
<td>3</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Total</td>
<td>66,459,947</td>
<td>142,483,508</td>
<td>208,943,456</td>
<td>100</td>
<td>100</td>
<td>100</td>
</tr>
</tbody>
</table>

Note: Includes only facilities reporting 204 chemicals common to both NPRI and TRI from selected industrial and other sources. Includes transfers of metals and metal compounds to energy recovery, treatment, sewage and disposal.

Source: Pollution Watch. 2010, p. 11
Table 2. Water Releases, by Basin, NPRI and TRI, 2007

<table>
<thead>
<tr>
<th>Basin</th>
<th>Water Releases</th>
<th>% of Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>NPRI (kg)</td>
<td>TRI (kg)</td>
</tr>
<tr>
<td>Lake Michigan</td>
<td>0</td>
<td>1,647,256</td>
</tr>
<tr>
<td>Lake Erie</td>
<td>358,708</td>
<td>1,143,649</td>
</tr>
<tr>
<td>Lake Ontario</td>
<td>133,268</td>
<td>1,299,453</td>
</tr>
<tr>
<td>St. Lawrence River</td>
<td>694,681</td>
<td>2,154</td>
</tr>
<tr>
<td>Lake Superior</td>
<td>110,095</td>
<td>917</td>
</tr>
<tr>
<td>Lake Huron</td>
<td>63,665</td>
<td>8,420</td>
</tr>
<tr>
<td>Total</td>
<td>1,360,416</td>
<td>4,101,849</td>
</tr>
</tbody>
</table>

Note: Includes only facilities reporting 204 chemicals common to both NPRI and TRI from selected industrial and other sources.

Source: Pollution Watch. 2010, p. 19

Table 3. On-Site Land Releases, by Basin, NPRI and TRI, 2007

<table>
<thead>
<tr>
<th>Basin</th>
<th>On-site Land Releases</th>
<th>% of Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>NPRI (kg)</td>
<td>TRI (kg)</td>
</tr>
<tr>
<td>Lake Erie</td>
<td>2,563,932</td>
<td>25,341,469</td>
</tr>
<tr>
<td>St. Lawrence River</td>
<td>10,446,238</td>
<td>0</td>
</tr>
<tr>
<td>Lake Ontario</td>
<td>5,170,248</td>
<td>766,124</td>
</tr>
<tr>
<td>Lake Michigan</td>
<td>0</td>
<td>4,609,433</td>
</tr>
<tr>
<td>Lake Huron</td>
<td>35,881</td>
<td>353,366</td>
</tr>
<tr>
<td>Lake Superior</td>
<td>12,284</td>
<td>272,699</td>
</tr>
<tr>
<td>Total</td>
<td>18,228,582</td>
<td>31,343,092</td>
</tr>
</tbody>
</table>

Note: Includes only facilities reporting 204 chemicals common to both NPRI and TRI from selected industrial and other sources. Since reporting for 2007, some of these facilities may have changed their name or ownership.

Source: Pollution Watch. 2010, p. 23
**COCs AND ONTARIO’S TOXICS REDUCTION STRATEGY**

The *Toxics Reduction Act, 2009*, is the cornerstone of Ontario’s Toxics Reduction Strategy (the Strategy). The goal of the Strategy is to help protect the health and environment of Ontarians by reducing toxic substances in air, land, water and consumer products while fostering the green economy. The Act requires regulated facilities to track and quantify the toxics that they use and create, to develop plans to reduce their toxics, and to make summaries of their plans available to the
Information collected through the reporting requirements of the Act and proposed regulations would be made available to the public so that Ontarians can be aware of toxic substances being used identified. Through a series of internal reviews and using the priority lists of others, 45 substances were identified. In 2009, an additional two substances, acetaldehyde and antimony and their compounds, were added after the ministry discovered and corrected a technical error in the ranking process. Additionally, the list of 47 substances and substance groups reflect the 2008 NPRI list of substances which includes additional individual substances in the PAH and dioxin and furan groupings. Tables 4 and 5 show these lists.

Table 4: Priority Toxics Screening: Ranking of Priority Toxics

<table>
<thead>
<tr>
<th>Substance</th>
<th>Total Score A</th>
<th>List B</th>
<th>Total Score 2</th>
<th>List C</th>
<th>Total Score 3</th>
<th>Rank</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lead &amp; compounds</td>
<td>485</td>
<td>533.5</td>
<td>640.2</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chromium &amp; compounds</td>
<td>482</td>
<td>530.2</td>
<td>636.24</td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Copper &amp; compounds</td>
<td>481</td>
<td>529.1</td>
<td>634.92</td>
<td>3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nickel &amp; compounds</td>
<td>477</td>
<td>524.7</td>
<td>629.64</td>
<td>4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cadmium &amp; compounds</td>
<td>474</td>
<td>521.4</td>
<td>625.68</td>
<td>5</td>
<td></td>
<td></td>
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<tr>
<td>Arsenic &amp; compounds</td>
<td>485</td>
<td>558.2</td>
<td></td>
<td>6</td>
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<td></td>
</tr>
<tr>
<td>Manganese &amp; compounds</td>
<td>483</td>
<td>476.3</td>
<td>579.6</td>
<td>7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Benzene</td>
<td>433</td>
<td>476.3</td>
<td>571.56</td>
<td>8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mercury &amp; compounds</td>
<td>428</td>
<td>470.8</td>
<td>564.96</td>
<td>9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Selenium &amp; compounds</td>
<td>426</td>
<td>468.6</td>
<td>562.32</td>
<td>10</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Toluene</td>
<td>389</td>
<td>427.9</td>
<td>513.48</td>
<td>11</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cyanides</td>
<td>415</td>
<td>458.7</td>
<td>498</td>
<td>12</td>
<td></td>
<td></td>
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<tr>
<td>Ethylbenzene</td>
<td>368</td>
<td>404.8</td>
<td>485.79</td>
<td>13</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Silver &amp; compounds</td>
<td>356</td>
<td>391.6</td>
<td>469.92</td>
<td>14</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tetrachloroethylene</td>
<td>351</td>
<td>386.1</td>
<td>463.32</td>
<td>15</td>
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<td>Xylene</td>
<td>417</td>
<td>458.7</td>
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<tr>
<td>Vanadium &amp; compounds</td>
<td>408</td>
<td>448.8</td>
<td>448.8</td>
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<tr>
<td>Hexachlorobenzene</td>
<td>326</td>
<td>358.6</td>
<td>430.32</td>
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<tr>
<td>Antimony &amp; compounds</td>
<td>389</td>
<td>427.9</td>
<td>427.9</td>
<td>19</td>
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<td>Cobalt &amp; compounds</td>
<td>305</td>
<td>335.5</td>
<td>402.6</td>
<td>20</td>
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<tr>
<td>Dichloroethane, 1,2-</td>
<td>317</td>
<td>310.2</td>
<td>372.24</td>
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<tr>
<td>Zinc &amp; compounds</td>
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<td>281.2</td>
<td>372.24</td>
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<td>Acetaldehyde</td>
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<td>298.1</td>
<td>357.72</td>
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<td>PAHs</td>
<td>271</td>
<td>298.1</td>
<td>357.72</td>
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<tr>
<td>Hexavalent chromium &amp; compounds</td>
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<td>298.1</td>
<td>357.72</td>
<td>25</td>
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<td></td>
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<tr>
<td>Formaldehyde</td>
<td>285</td>
<td>57</td>
<td>342</td>
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<tr>
<td>Phenol</td>
<td>278</td>
<td>55.6</td>
<td>333.6</td>
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<tr>
<td>Biphenyl</td>
<td>331</td>
<td>331</td>
<td></td>
<td>28</td>
<td></td>
<td></td>
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<tr>
<td>Chlorine</td>
<td>319</td>
<td>319</td>
<td></td>
<td>29</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hydrochloric acid</td>
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<td>305</td>
<td></td>
<td>30</td>
<td></td>
<td></td>
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<tr>
<td>Vinyl chloride</td>
<td>219</td>
<td>240.9</td>
<td>289.08</td>
<td>31</td>
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<tr>
<td>Triethylene</td>
<td>288</td>
<td>288</td>
<td></td>
<td>32</td>
<td></td>
<td></td>
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<tr>
<td>Aluminium</td>
<td>283</td>
<td>283</td>
<td></td>
<td>33</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Methanol</td>
<td>254</td>
<td>254</td>
<td></td>
<td>34</td>
<td></td>
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</tr>
</tbody>
</table>

*PAH grouping includes all individual PAH compounds on NPRI.

Table 5. Priority Toxics Screening: Carcinogens

<table>
<thead>
<tr>
<th>Substance</th>
<th>Chemical Abstract Service Number (CASN)</th>
<th>Classification</th>
</tr>
</thead>
<tbody>
<tr>
<td>p,p’-methylenebis(2-chloroaniline)*</td>
<td>101-14-4</td>
<td>IARC Group 2A</td>
</tr>
<tr>
<td>Acrylamide*</td>
<td>79-06-1</td>
<td>IARC Group 2A</td>
</tr>
<tr>
<td>Aluminum Production</td>
<td>7429-90-5</td>
<td>IARC Group 1</td>
</tr>
<tr>
<td>Arsenic and compounds</td>
<td></td>
<td>IARC Group 1, NTP (known)</td>
</tr>
<tr>
<td>Asbestos*</td>
<td>1332-21-4</td>
<td>IARC Group 1, NTP (known)</td>
</tr>
<tr>
<td>Benzene</td>
<td>71-43-2</td>
<td>IARC Group 1, NTP (known)</td>
</tr>
<tr>
<td>1,3 -Butadiene*</td>
<td>106-99-0</td>
<td>IARC Group 2A, NTP (known)</td>
</tr>
<tr>
<td>Cadmium and compounds</td>
<td></td>
<td>IARC Group 1, NTP (known)</td>
</tr>
<tr>
<td>Chlorinated toluenes*</td>
<td></td>
<td>IARC Group 2A</td>
</tr>
<tr>
<td>Benzoic acid</td>
<td>98-88-4</td>
<td>IARC Group 2A</td>
</tr>
<tr>
<td>Benzyl chloride</td>
<td>100-44-7</td>
<td>IARC Group 2A</td>
</tr>
<tr>
<td>Creosote*</td>
<td>8001-58-9</td>
<td>IARC Group 2A</td>
</tr>
<tr>
<td>Dioxins and Furans*</td>
<td></td>
<td>IARC Group 1, NTP (known)</td>
</tr>
<tr>
<td>Epichlorohydrin</td>
<td>106-89-8</td>
<td>IARC Group 2A</td>
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<tr>
<td>Ethylene Oxide*</td>
<td>75-21-8</td>
<td>IARC Group 1, NTP (known)</td>
</tr>
<tr>
<td>Formaldehyde</td>
<td>50-00-0</td>
<td>IARC Group 1</td>
</tr>
<tr>
<td>Hexavalent chromium and compounds</td>
<td></td>
<td>IARC Group 1, NTP (known)</td>
</tr>
<tr>
<td>Lead and compounds</td>
<td></td>
<td>IARC Group 2A</td>
</tr>
<tr>
<td>Nickel and compounds</td>
<td></td>
<td>IARC Group 1, NTP (known)</td>
</tr>
<tr>
<td>Styrene Oxide*</td>
<td>96-09-3</td>
<td>IARC Group 2A</td>
</tr>
<tr>
<td>Sulfuric Acid and compounds*</td>
<td></td>
<td>IARC Group 2A</td>
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<tr>
<td>Sulfuric acid</td>
<td>7664-93-9</td>
<td>IARC Group 1, NTP (known)</td>
</tr>
<tr>
<td>Dimethyl sulphate</td>
<td>77-78-1</td>
<td>IARC Group 2A</td>
</tr>
<tr>
<td>Diethyl sulphate</td>
<td>64-67-5</td>
<td>IARC Group 2A</td>
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<tr>
<td>Tetrachloroethylene</td>
<td>127-18-4</td>
<td>IARC Group 2A</td>
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<tr>
<td>Thorium Dioxide*</td>
<td>1314-20-1</td>
<td>NTP (Known)</td>
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<td>Tetrachloroethylene*</td>
<td>79-01-6</td>
<td>IARC Group 2A</td>
</tr>
<tr>
<td>Total PAHs**</td>
<td></td>
<td>IARC Group 1 and Group 2A</td>
</tr>
<tr>
<td>Vinyl chloride</td>
<td>75-01-4</td>
<td>IARC Group 1, NTP (known)</td>
</tr>
</tbody>
</table>

* 13 carcinogens added based on their carcinogenicity only.

**Benzo(a)pyrene and Dibenzo(a,h)anthracone

IARC: The International Agency for Research on Cancer (IARC).
Group 1 - The agent (mixture) is carcinogenic to humans.
Group 2A - The agent (mixture) is probably carcinogenic to humans.

NTP: U.S. Department of Health and Human Services, Public Health Service, National Toxicology Program defines agents as known or reasonably carcinogenic.


**PERFLUOROOCTANESULFONATE (PFOS) and PERFLUOROOCTANOIC ACID (PFOA)**

PFOS and PFOAs are either synthetically produced or metabolized from other per fluorinated chemicals (PFC) and have been categorized as persistent organic pollutants (POP). PFOS has been used in surfactants such as water repellent coatings (i.e., Scotchgard™) and fire suppressing foams, as well as many consumer products (i.e., non-stick pans, furniture, shampoos, etc.). They have a slow degradation process in humans, requiring 4 years to metabolize and having a half life of 5 years.
Traces of these substances have been found in the sera of pregnant women and their newborn babies, as well as in breast milk. This presents concerns for persistence, bioaccumulation, and toxicity (Thomson et al., 2010).

Recent studies have reported that human milk consumption is the main route of exposure to PFOS and PFOAs for newborns, resulting in those individuals exceeding the dietary exposure at a later age. It should be noted that other POPs, such as PCB and PBDEs, are known to be persistent lipophilic pollutants. PFCs, however, are associated with proteins; their effects on the maternal body are not presently known. A recent study compared PFC in breast milk and serum finding the amount of PFC in breast milk to be 2 magnitudes lower, which is still regarded as a major source of exposure for an infant. Tolerable daily intake (TDI) for PFOA and PFOS were established within the European Food Safety Authority (EFSA), with daily intakes of 1.5 μg/kg body weight/day and 150 ng/kg body weight/day, respectively. TDI were created for long term purposes and would not be fit for breast-feeding infants (EFSA, 2008).

There have been studies identifying an inverse relationship between PFOS and PFOA and birth weight, newborn head circumference, crown-heel length, and ponderal index. But it must be taken into consideration that the study was conducted in regards to cord blood samples taken after the delivery. Another study had results of the PFOA maternal plasma being inversely related to birth weight. This could be a result of the PFOA more readily crossing the placenta barrier in comparison to PFOS. Although there was not a specific dose-response relation, it is clear that the results are associated with the outcomes of a threshold effect (Fei et al., 2007).

**FLAME RETARDENTS**

Flame retardant (FR) chemicals, which are designed to slow a flame’s duration and propagation, have been applied to commercial products since the 19th century. The apparent effectiveness of FRs has resulted in worldwide applications in various products including clothing, furniture, electronics, and components for the transportation industry. Undoubtedly, the most successful class of FRs is the one based on bromine; the labile carbon-bromine bond easily avails itself during combustion, scavenging oxygen-containing radicals that ultimately suffocates the flame. However, the widespread use has led to other unintended outcomes. For example, some of the congeners of polybrominated diphenyl ethers (PBDEs) are known to fulfill all three criteria of persistence, toxicity, and bioaccumulation. This has led to their recent inclusion in the Stockholm Convention on Persistent Organic Pollutants (Sverko et al., 2010).

**Brominated Flame Retardents**

*Polybrominated Diphenyl Ethers (PBDE)*

PBDEs are a group of synthetic organic chemicals with no known natural sources in the environment, except for a few marine organisms that produce forms of PBDEs that contain higher levels of oxygen. They are ubiquitous, sufficiently persistent and bio accumulative. The first commercial production of PBDEs began in the 1970s in Germany. They can constitute by weight up to 30% of many consumer
products. Some of the major sources of these chemicals, found in both homes and the workplace, include textiles, furniture, plastic compounds, circuit boards and building materials. They are also used as components in plastics, and are released from plastic products, and are known as endocrine-disrupting compounds (EDCs) owing to their ability to modulate the endocrine system. The detection of EDCs in the environment, biota and humans is of concern due to their potential to interfere with the physiology of living organisms. PBDEs enter the environment as mixtures containing a variety of individual brominated diphenyl ether components, known as congeners (Talsness et al., 2009).

The presence of PBDEs in breast milk, adipose tissue and serum has been confirmed in several studies. An examination of a cohort of 4-year-old children revealed that breast-fed children have 6.5 times higher average body burden of total PBDEs than formula-fed children. Detection of PBDEs in liver tissue of human fetuses and in cord blood demonstrates that in utero exposure is taking place. On a per-kilogram basis, studies have described higher levels of exposure to PBDEs for children than adults (Talsness et al., 2009).

It is known that diseases of the thyroid gland affect the reproductive capacity of women. In particular, hypothyroid women may exhibit anovulation, and hypothyroidism is associated with hyperprolactinaemia, which inhibits the release of pituitary gonadotropin and gonadal steroids. Although less is known about the role of thyroid hormones in the development of the reproductive system, it is believed that they are important for gonad development in both sexes. Animal studies and in vitro studies demonstrate that PBDEs interfere with thyroid hormone action, and the function of both the ovary and the testis has been altered following in utero exposure to PBDEs. Thyroid hormones indirectly affect sperm production by regulating the number of Sertoli cells, which act as nurse cells for developing sperm. In the ovary, thyroid hormone receptors are present in granulosa cells, which produce steroids and provide growth factors interacting with the oocyte (Talsness et al., 2009).

A larger study regarding in utero and early developmental exposure to PBDEs with cryptorchidism involved 86 Danish and Finnish newborn boy–mother pairs. Associations between PBDE contamination of human breast milk and cryptorchidism and increased gonadotropin release to support normal testosterone production were observed. Although there was no significant difference in the placental concentrations, the sum of PBDEs in breast milk was higher in cryptorchid boys than in controls and was positively correlated with infant serum luteinizing hormone concentration. Talsness et al. (2009) suggest that the lack of correlation between the PBDE concentrations in the placental and breast milk samples may be that the placenta represents the situation at delivery as one would find in a single blood sample and not for long-term exposure (Talsness et al., 2009).

Thyroid hormone is crucial for growth and development and, in particular, for neurodevelopment. Decreases in fetal and maternal thyroid hormone are known to impact neuropsychological development in humans, and impaired achievement on neuropsychological tests can occur even when maternal hypothyroidism is subclinical. Data regarding neurotoxicants indicate that there is a continuum of toxic outcomes at low doses (i.e., chronic daily exposures) which do not induce overt clinical symptoms. Talsness et al. (2009) suggest that neurodevelopmental disorders associated with exposure to known human neurotoxicants and untested chemicals have resulted in a veiled pandemic, incurring significant costs to society because of lowered productivity and reductions in intelligence (Talsness et al., 2009).
Hexabromocyclododecane (HBCD)

Hexabromocyclododecane (HBCD) is another type of brominated flame retardant. They are also commonly used in household items and electronics and have been detected in the environment and/or human body fluids, including those of children. It has been suggested that HBCD could have endocrine disruptive and neurotoxic effects. Impaired oligodendroglial development in the brain, impairment in learning and memory, and aberrant spontaneous behavior have also been reported. There are very few studies focused specifically on the effects of HBCD, as many of their effects are similar to PBDEs, which has a stronger presence effect in the environment and on human health (Ibhazehiebo et al., 2011).

Chlorinated Flame Retardents

Chlorinated flame retardants, like brominated flame retardants, have been detected in the environment and caused concern due to their bioaccumulation in biota, and persistence in sediment. Chlorinated compounds continue to be used as flame retardants, but to a lesser extent than brominated compounds. Short-chain chlorinated paraffins (SCCPs) and medium-chain chlorinated paraffins (MCCPs) are used as flame retardants and plasticizers in vinyl plastics, rubber, paints, adhesives, and sealants. SCCPs have been termed persistent toxic substances by the United Nations Environment program. Furthermore, Environment Canada recently concluded that both SCCPs and MCCPs are toxic to the environment and human health as defined under the Canadian Environmental Protection Act (Ismail et al., 2008).

A recent flame retardent of interest is Dechlorane Plus (DP). Using high-resolution mass spectrometry, a number of mass spectra peaks appeared to be from unknown compounds related to DP. These compounds were found to be in trout, where they had 2 magnitude levels higher than the concentration of just DP. Researchers are now focusing on the widespread effects throughout the food chain (Betts, 2010).

Unfortunately, the problems with chlorinated flame retardents do not stop with their production and use. Uncontrolled burning and dismantling/recycling of electronic and electric waste in developing countries results in contamination and formation of brominated and chlorinated dioxins and furans; these substances are highly toxic, thus causing increased concern both for the health of individuals and for the environment (Birnbaum, 2010).

PCB

Polychlorinated biphenyls (PCBs) are ubiquitous environmental toxins. Improper disposal has been a major source of environmental contamination. Their production and use were banned in most industrialized countries in the late 1970s because of toxic effects in wildlife. PCBs have been shown to have toxic effects on various organs including tissues of the nervous, reproductive, and immunologic systems. They bioaccumulate due to their lipid solubility and biodegradability through the food chain to give rise to their presence in human body fluids and tissues, and are a source of public health
concern. Breastfeeding can decrease a mother's body burden of these compounds. On the other hand, it results in the exposure of the baby (Park et al., 2010).

A recent study identified that women who failed to conceive (nulliparas) had significantly longer attempt times, higher in utero exposure to PCB congeners associated with a higher PCB score than either primiparas or multiparas women. PCB exposure continues globally due to widespread soil contamination and bioaccumulation. More than two thirds of 1.2 million tons of PCBs produced worldwide is either still in use or waiting for disposal, presenting a significant, global, public policy challenge. Recent studies document continuing perinatal exposure to PCBs. The PCB dilemma could be a model for other contemporary persistent organic pollutants, particularly those that share structural similar it is with PCBs, such as polybrominated diphenylethers, PBDEs. Exposures in utero could affect reproduction and fertility through multiple alternative mechanisms which operate during fetal life. Among the many potential mechanisms are influences on the structure and function of the uterus or fallopian tubes as was observed following prenatal exposure to the potent estrogen diethylstilbestrol; impacts on oogenesis and cell death in the human ovary during fetal life that could alter the size of the ovarian reserve in adult life and possibly the quality of the oocyte destined to become the conceptus; disturbance of maternal and therefore fetal thyroid function that persists and later disrupts menstrual cycling and fertility in the daughter or disruption of sexually dimorphic patterns in the hypothalamus pituitary gonadalax is during early development (Cohn et al., 2011).

As previously mentioned, PCBs have been shown to have toxic effects on various organs including tissues of the nervous, reproductive, and immunologic systems. Although there is growing evidence from in vivo and in vitro studies to support the hypothesis of adverse effects of PCBs on neurodevelopment, the mechanisms are not well understood. Additionally, various epidemiological studies have found an association between PCB exposure and decreased cognitive development. The most well-known mechanism related to adverse health effects such as immune suppression, hepatotoxicity, and thymic atrophy is aryl hydrocarbon (Ah) receptor-mediated pathways for dioxin-like PCBs. Since non-dioxin-like PCBs have shown low affinity for the Ah receptor, they have been regarded as potentially less toxic. However, neurotoxicity, carcinogenicity, and changes in hormones have also been described as resulting from non-dioxin-like PCBs (Park et al., 2010).

Barrett (2010) uses the backdrop of routine childhood immunizations to explore the developmental immunotoxicity of PCBs, finding that higher PCB exposure in toddlerhood is associated with reduced antibodies against diphtheria and tetanus later in childhood. Analysis revealed inverse relationships between PCB concentrations at different time points and antibody concentrations. However, higher PCB concentrations in mother’s milk samples collected after birth and in children’s blood samples at 18 months were clearly associated with lower levels of diphtheria antibodies in the children at age 5. Researchers point out that early-life PCB exposure may increase the risk of incomplete protection against diphtheria and possibly tetanus even if a child receives a full schedule of vaccinations (Barrett, 2010).

**BISPHENOL A (BPA)**

Bisphenol A (BPA) is one of the highest volume chemicals produced worldwide. In 2008, global production was over 5.2 million metric tons, with a projected 5% growth in demand expected each
year (ICIS Chemical Business, 2009). It is used to manufacture polycarbonate plastics and resins. The resin is applied to most food and beverage interiors to prevent metal contamination (Health Canada, 2008). Polycarbonate plastics are lightweight, durable, with high heat and electrical resistance. They are used in a wide range of products including digital media, electronics, electrical and sports equipment, automobiles, and medical devices (Canadian Plastic Industry Association, 2009). BPA has been measured in surface and groundwater, sediments, landfill leachate, and biota implying high and/or continuous inputs into the environment (Health Canada, 2008). Detectable levels have been found in the vast majority of individuals sampled (Vandenbarg et al., 2007), with some suggesting more than 90% of the population is exposed (Calafet et al., 2008; Bushnik et al., 2010). BPA has been identified as an endocrine disruptor (which can cause reproductive abnormalities) (Maffini et al., 2006). Vom Saal and Hughes (2005) review a range of studies that have observed health effects within laboratory animals from low-doses of exposure which include changes in rates of growth and sexual maturation, hormone levels in blood, decreased fertility, suppressed immune function, changes in brain chemistry and behavior including increased hyperactivity and aggressiveness, and impaired learning. Lang et al. (2008) have reported associations with cardiovascular disease, diabetes and liver-enzyme abnormalities.

BPA is one of the substances reviewed under Canada’s Chemicals Management Plan. Health Canada’s risk assessment of exposures from dietary sources during infant development, determined that primary exposure is through polycarbonate baby bottles and migration of BPA from cans into infant formula (2008). The findings indicated that most Canadians need not be concerned because health effects occur at much greater levels than to what people are exposed. Yet a limited number of studies suggest enhanced sensitivity and exposure amongst infants and fetuses. Consequently the Government of Canada adopted a precautionary approach proposing to reduce infant exposure by banning the importation and sale of polycarbonate baby bottles, developing alternative infant formula packaging with industry, and declaring BPA as ‘toxic’ under the Canadian Environmental Protection Act.

Up until very recently, Canada was the only country in the world to take regulatory action on this chemical. The decision contrasts with other risk assessments carried out by the U.S. Food and Drug Administration (FDA) - (recently pressured to re-examine their position), and the Japan National Institute of Advanced Industrial Science and Technology. As recently as September 2010, The European Food Safety Authority concluded that based on existing evidence the established ‘tolerable daily intake’ remains safe. Yet, two months later the European Union Executive Commission announced plans to ban BPA from baby bottles by June 2011. Hence, there is considerable inconsistency with respect to perceived risks, policy, and regulatory responses despite access to the same evidence-base. Significant uncertainties across the current evidence-base fuel political controversy and opposing policy responses.

Science assessing the health risks of BPA is contentious, particularly with respect to ascertaining human health effects from low doses of exposure. For fifty years, the safety of BPA and chemicals in general, was predicated on the presumption of a monotonic dose–response relationship (Vogel, 2009). That is, the higher the dose, the greater the effect, suggesting that at a particular low dosage hazardous effects become minimal or non-existent. However, a growing body of research on endocrine disruption is challenging this assumption and associated methodological practices (e.g., Welshons et al., 2003), despite significant resistance and criticism from industry and some segments
As explained by Vom Saal and Hughes (2005), the U.S. Environmental Protection Agency (EPA) considers “low-dose” effects of endocrine-disrupting chemicals as effects reported at doses lower than those used in traditional toxicological studies conducted for risk assessment purposes. For BPA specifically, the lowest dose typically studied is 50 mg/kg/day, the currently accepted lowest observed adverse effect level (LOAEL) used to calculate a reference dose (the level at which there is unlikely any deleterious effects over a lifetime) of 50 μg/kg/day (2005). Throughout the 1990s, controversy existed between reports claiming effects from BPA at low doses, and others, some of which were industry funded, that disputed these claims (Vogel, 2009). In 2000, the EPA asked the National Toxicology Program (NTP)—a U.S. government program providing scientific information to government agencies, NGOs, and the public on chemical toxicity—to investigate the low-dose issue. They concluded there was “credible evidence” for low-dose effects below current safety standards (NTP, 2001).

In response, the Harvard Center for Risk Analysis (HCRA) performed a weight-of-the-evidence evaluation of available data on developmental and reproductive effects of low-dose exposures to BPA on laboratory animals. They concluded that evidence for low-dose effects is by and large weak, irrelevant to humans and unreliable (Gray et al., 2004). However, concerns around the objectivity of these findings have been raised given that the HCRA has received financial support from the American Chemistry Council, the Society of the Plastics Industry, Dow Chemical Company, the Business Roundtable, Phillip Morris, and General Electric (Vogel, 2009).

The following year, Vom Saal and Hughes disputed the integrity of these findings, stating that adverse effects from low-dose exposures have been demonstrated in many published studies. They claimed that the HCRA panel only analyzed 19 of the 47 available published studies at the time, and within the two years it took for publication, many more articles were released reporting low-dose effects (2005). Vom Saal and Hughes concluded that out of 115 studies involving low doses, 94 reported significant effects. They also argued that source of funding was highly correlated with positive or negative findings with ninety percent of government funded studies reporting significant effects at doses of 50mg/kg/day, while 0% of industry funded studies reported significant effects. They and others (e.g., Welshons et al., 2003) assert that new evidence challenges many basic assumptions underlying conventional risk assessment methods and discourse. They suggest a wider range of doses be examined not just a few high doses as extrapolation based on a linear-threshold model is invalid for endocrine-disrupting chemicals.

Goodman et al. (2006), funded by the American Plastics Council, conducted another weight-of-evidence assessment, which included over fifty additional recently published studies. Their findings were consistent with the HCRA’s conclusions that existing evidence does not suggest low oral doses of BPA are detrimental to human health. They argued those concluding otherwise have not critically assessed the rigour and reliability of existing evidence and stressed that industry-funded studies are subject to the same peer review as publicly-funded research. The American Chemistry Council’s Polycarbonate/BPA Global Group also discredits research supporting the low-dose hypothesis (2009).

In 2006, the U.S. National Institute of Health (NIH) convened a panel of 38 international experts to analyze BPA risks. The panel assertively concluded that “the wide range of adverse effects of low doses in laboratory animals exposed both during development and in adulthood is great cause for
concern with regard to the potential for similar adverse effects in humans” (emphasis added) (Vom Saal et al., 2007, p.136). They list specific trends in human diseases that relate to the adverse effects observed in experimental animals including increases in prostate and breast cancer, uro-genital abnormalities in males, early onset of puberty in girls, metabolic disorders, and neurobehavioral problems (2007). They concede that few epidemiological studies have directly examined potential effects from BPA on human health, and that more research is needed.

In 2007, the NTP revisited the issue, and came to more conservatively expressed conclusions than the NIH-funded panel, stating only “some” level of concern regarding neurological effects from exposures of fetuses, infants, and children to low-doses of BPA, and “minimal concerns” regarding effects on the mammary gland, and early onset of puberty in females (Polycarbonate/BPA Global Group, 2009; Ericson, 2008). For adults the NTP expressed “negligible concern” for reproductive effects. The NTP also stressed that many studies demonstrating low-dose effects are controversial due to insufficient replication by independent investigators, questionable experimental approaches, and disagreement over the relevance of using animal models to evaluate human health risks (BPA Global Group, 2009).

It was discovered that Sciences International, the consultants that summarized the research on behalf of the NTP, had previously done work for BPA manufacturers Dow and BASF (Layton and Lee, 2008). After mounting allegations, the NTP cancelled its contract with the firm and reexamined the literature, including several other low-dose studies omitted from the initial review (Ericson, 2008; Schierow and Lister, 2008). In the final report, the NTP maintained similarly cautiously worded conclusions.

Health Canada released its risk assessment of BPA in April, 2008. It embraced a more precautionary approach, concluding sufficient evidence suggests that periods of early development are sensitive to BPA effects, and while exposure levels are below those known to cause effects, it is better to be safe than sorry approach based on the avoidance of hazard.

Some members of U.S. congress have turned their attention towards this issue in response to rising media attention. In April 2008, the FDA formed an agency-wide BPA task force to facilitate yet another review of the research. While this review is ongoing, the FDA maintains that a large body of evidence indicates that products on the market containing BPA are safe, (despite recently admitting “some concern” for effects upon children) (FDA, 2010). Conclusions from risk assessments conducted by the European Food Safety Authority, and the Japanese National Institute of Advanced Industrial Science and Technology are in line with this position. Nevertheless, some U.S. jurisdictions, e.g., Suffolk County in New York State as well as the states of Wisconsin, Minnesota, Washington, Maryland, Connecticut and the City of Chicago have enacted bans of BPA in at least baby bottles, and in some cases other children’s products. Retailers are also no longer stocking plasticized baby bottles. At the Federal level Congressman Edward Markey introduced a bill aiming to ban BPA from food containers. It is currently being reviewed by the House Committee on Energy and Commerce (GovTrack.US, 2010).
VOLATILE ORGANIC COMPOUNDS (VOCs) & POLYAROMATIC COMPOUNDS (PAHs)

Volatile Organic Compounds

VOCs are organic compounds containing one or more carbon atoms that have high vapour pressures and therefore evaporate readily to the atmosphere. There are literally thousands of compounds that meet this definition, but most programs focus on the 50 to 150 most abundant compounds containing two to twelve carbon atoms. VOC do not include photochemically non-reactive compounds such as methane, ethane and the chlorofluorocarbons (CFC) (Environment Canada, 2010a). VOCs include a variety of chemicals, some of which may have short- and long-term adverse health effects. Concentrations of many VOCs are consistently higher indoors (up to ten times higher) than outdoors. VOCs are emitted by a wide array of products numbering in the thousands. Examples include: paints and lacquers, paint strippers, cleaning supplies, pesticides, building materials and furnishings, office equipment such as copiers and printers, correction fluids and carbonless copy paper, graphics and craft materials including glues and adhesives, permanent markers, and photographic solutions (Health Canada, 2009).

Health effects include eye, nose, and throat irritation; headaches, loss of coordination, nausea; damage to liver, kidney, and central nervous system. Some organics can cause cancer in animals; some are suspected or known to cause cancer in humans. Key signs or symptoms associated with exposure to VOCs include conjunctival irritation, nose and throat discomfort, headache, allergic skin reaction, dyspnea, declines in serum cholinesterase levels, nausea, emesis, epistaxis, fatigue, dizziness (Health Canada, 2009).

The ability of organic chemicals to cause health effects varies greatly from those that are highly toxic, to those with no known health effect. As with other pollutants, the extent and nature of the health effect will depend on many factors including level of exposure and length of time exposed. Eye and respiratory tract irritation, headaches, dizziness, visual disorders, and memory impairment are among the immediate symptoms that some people have experienced soon after exposure to some organics. At present, not much is known about what health effects occur from the levels of organics usually found in homes. Many organic compounds are known to cause cancer in animals; some are suspected of causing, or are known to cause, cancer in humans (Environment Canada, 2010a).

Some VOCs, especially the BTEX compounds (i.e., benzene, toluene, ethylbenzene, and xylenes), are widely recognized as human carcinogens. Accidents and spills have been used to examine the impact of relatively high doses. The health effects of exposure to BTEX in the Taean area, Korea, after the Hebei Spirit oil spill were evaluated. It was found that pregnant women who lived near the accident site reported more symptoms of eye irritation and headache than those who lived farther from the site. There was a trend of decreasing symptoms with an increase in distance from the spill site. Pregnant women exposed to higher ambient cumulative levels of xylene were significantly more likely to report symptoms of the skin in the first day after the accident and significantly more likely to report abdominal pain during the 1st through 4th days following the accident. This study suggests that exposure to BTEX from an oil spill is correlated with an increased risk of health effects among pregnant women (Kim et al., 2009).
Traffic related VOC pollution is a more serious problem in developing countries than in North America and Europe. Evidence shows that private cars and taxis are more problematic than buses and trains. Indeed, exposure to volatile organic compounds has long been associated with adverse health conditions such as atrophy of skeletal muscles, loss of coordination, neurological damage, dizziness, throat, nose, and eye irritation, nervous system depression, liver damage, and respiratory symptoms. Twenty-six species of ambient VOCs were monitored during a 2-week period in September, 2008 at 100 sites across Windsor and Detroit. Ten species with highest concentrations were selected for further investigation; toluene, (m+p)-Xylene, hexane, benzene, 1,2,4-Trimethylbenzene, dichloromethane, ethylbenzene, o-Xylene, n-Decane, and 1,3,5-Trimethylbenzene. Comparison to a similar investigation in Sarnia, Ontario in October 2005 revealed that the mean concentrations of VOCs were higher in Windsor-Detroit for all species by a significant margin (31-958%), indicating substantial impact of local industrial and vehicular emissions in the Windsor/Detroit area. For most VOCs, the concentrations were higher in Detroit than in Windsor. The mean concentration of total VOC was 9.7 μm/m³ in Windsor, which is slightly higher than that in Sarnia in 2005 (7.9 um/m³), whilst total VOC concentration in Detroit was much higher (16.5 μm/m³). There were strong correlations among several of the 10 species, with the highest amongst the BTEX (benzene, toluene, ethylbenzene, and xylenes) group, suggesting common sources of these species (Brook et al., 2008).

Chlorinated and aromatic solvents (trichloroethylene (TCE), benzene) have been shown to enter drinking water supplies from leaking underground storage tanks, landfill, and other waste disposal facilities. One particularly strong case study involving contaminated drinking water was documented by Lagakos et al. (2002). After toxic industrial solvents (mainly TCE and benzene) were identified in the municipal drinking water of Woburn, Massachusetts, a cluster of childhood leukemia was reported by the residents. Lagakos et al. (2002) compiled residential exposure scores to examine the relation between the fraction of the water supply coming from contaminated wells and the incidence of childhood leukemia, perinatal deaths, congenital anomalies and childhood disorders. The results identified a significant excess of leukemia and associations with eye/ear congenital anomalies and central nervous system/oral cleft/chromosomal anomalies (mostly Downs Syndrome). Due to chlorination of private and public swimming pools, children who swim have an increased risk of developing asthma and infections of the respiratory tract and ear. A 1.6 to 2.0 fold increased risk for bladder cancer has been associated with swimming or showering/bathing with chlorinated water. TCE is also suspected to play a role in autoimmune diseases (see Cooper et al., 2009), although doubt remains of its link to congenital heart disease (see Watson et al., 2006).

Rowe et al. (2007) examined the occurrence of individual and multiple VOCs and assessed the potential human-health relevance of VOC concentrations. They detected VOCs in 65% of the samples; about one-half of these samples contained VOC mixtures. Frequently detected VOCs included chloroform, toluene, 1,2,4-trimethylbenzene, and perchloroethylene. VOC concentrations generally were < 1 μg/L. Drinking water supplied by domestic wells is vulnerable to low-level VOC contamination. About 1% of samples had concentrations of potential human-health concern.

VOC exposure also results from landfill sites. For example, Urase et al. (2008) examined the emission of VOCs from a solid waste disposal site for municipal solid wastes. The VOCs contained in the landfill gas taken at the site were benzene, toluene, xylenes, ethyl benzenes, and trimethyl benzenes, while the concentrations of chlorinated compounds were very low. The concentration of benzene in the landfill gas samples ranged from below the detection limit to 20 mg m⁻³, and the ratio of benzene to
toluene ranged from 0.2 to 8. The higher concentrations of VOCs in landfill gas and in leachates were observed with the samples taken at high temperature areas of the target site. Polystyrene plastic waste was identified as one of the sources of VOCs in solid waste disposal sites at a high temperature condition. The appropriate heat management in landfill sites is an important countermeasure to avoid unusually high emission of VOCs because the heat generated by the biodegradation of organic solid wastes may promote the release of VOCs, especially in the case of sites which receive both biodegradable and plastic wastes.

There appears to be a relationship between the release of VOCs and Sick Building Syndrome (SBS) with employee complaints of eye irritation, sore throats and other unspecific symptoms. VOCs are present in buildings, particularly in new or recently refurbished buildings. They are typically associated with materials derived from petroleum products and arise in off-gassing from a variety of building products, furnishings, cleaning products, paints, adhesives, carpeting, upholstery, paneling, plastic, vinyl, copying machines, computers and hundreds of other office products. VOCs are emitted in varying amounts by the lubricating oil in mechanical parts of office printers. These include substances such as benzene and formaldehyde, which in low concentrations can cause skin irritation and dry throats but in higher concentrations are linked to cancer.

A recent review indicates that there is added evidence for the role of personality traits and psychosocial work environment, reactive chemistry and the inflammatory properties of indoor particles for SBS. Field studies using physiological methods and measurements of oxidative stress can lead to better understanding of the cause of SBS. Moreover, there is an increased focus on the indoor environment and 'sick house syndrome' in Asia. Overall, the researchers found an irritation of the mucous membranes and a reduction of well being (Hutter et al., 2006). These results held even when the levels of VOCs were measured to be fairly low.

**Figure 5. 2000 VOC Emissions**

Polycyclic Aromatic Hydrocarbons

There are several hundred different forms of PAH, and sources can be both natural and man-made. They are widespread in distribution. PAHs can cause cancer. Sources of 1,3 butadiene include the manufacturing of synthetic rubbers, petrol driven vehicles and cigarette smoke. There is an apparent correlation between butadiene exposure and a higher risk of cancer. PAHs are lipophilic, meaning they mix more easily with oil than water. The larger compounds are less water-soluble and less volatile (i.e., less prone to evaporate). Because of these properties, PAHs in the environment are found primarily in soil, sediment and oily substances, as opposed to in water or air. However, they are also a component of concern in particulate matter suspended in air. Natural crude oil and coal deposits contain significant amounts of PAHs, arising from chemical conversion of natural product molecules, such as steroids, to aromatic hydrocarbons. They are also found in processed fossil fuels, tar and various edible oils. In addition to their presence in fossil fuels they are also formed by incomplete combustion of carbon-containing fuels such as wood, coal, diesel, fat, tobacco, and incense. Different types of combustion yield different distributions of PAHs in both relative amounts of individual PAHs and in which isomers are produced. Thus, coal burning produces a different mixture than motor-fuel combustion or a forest fire, making the compounds potentially useful as indicators of the burning history. Hydrocarbon emissions from fossil fuel-burning engines are regulated in developed countries (ATSDR, 2011).

PAHs known for their carcinogenic, mutagenic and teratogenic properties are benz(a)anthracene and chrysene, benzo(b)fluoranthene, benzo(j)fluoranthene, benzo(k)fluoranthene, benzo(a)pyrene, benzo(ghi)perylene, coronene, dibenz(a,h)anthracene, indeno(1,2,3-cd)pyrene and ovalene. High prenatal exposure to PAH is associated with lower IQ and childhood asthma. The Center for Children’s Environmental Health cohort demonstrates that exposure to PAH pollution during pregnancy is related to adverse birth outcomes including low birth weight, premature delivery, and heart malformations. Cord blood of exposed babies shows DNA damage that has been linked to cancer. Follow-up studies show a higher level of developmental delays at age three, lower scores on IQ tests and increased behavioral problems at ages six and eight. The major route of exposure to PAHs in the general population is from breathing ambient and indoor air, eating food containing PAHs, smoking cigarettes, or breathing smoke from open fireplaces. Tobacco smoke contains a variety of PAHs, such as benzo(a)pyrene, and more than 40 known or suspected human carcinogens. For non-smokers the main route of exposure is through food. PAH concentrations in foodstuffs vary. Charring meat or barbecuing food over a charcoal, wood, or other type of fire greatly increases the concentration of PAHs. Some crops, such as wheat, rye, and lentils, may synthesize PAHs or absorb them via water, air, or soil. Water can also contain substantial amounts of PAHs since those chemicals can leach from soil into water or they can enter water from industrial effluents and accidental spills during oil shipment at sea. Soil also contains PAHs, primarily from airborne fallout (Columbia Center for Children's Health, 2010).

PAH exposure occurs on a regular basis for most people. Occupational exposure may also occur in workers breathing exhaust fumes, such as mechanics, street vendors, motor vehicle drivers, as well as those involved in mining, metal working, or oil refining. Routes of exposure include ingestion, inhalation, and dermal contact in both occupational and non-occupational settings. Some exposures may involve more than one route simultaneously, affecting the total absorbed dose (such as dermal
and inhalation exposures from contaminated air). Children have similar exposures to adults, although developing biological systems and places of play may complicate matters (Perera et al., 2009).

Prenatal exposure has also become a recent concern. Edwards et al. (2010) investigated the relationship between prenatal PAH exposure and child intelligence at 5 years of age, controlling for potential confounders suspected to play a role in neurodevelopment. A cohort of pregnant, healthy, nonsmoking women was enrolled in Krakow, Poland, between 2001 and 2006. They found that higher prenatal exposure to airborne PAHs was associated with decreased IQ points at 5 years of age, after adjusting for potential confounding variables. These results suggest that prenatal exposure to airborne PAHs adversely affects children’s cognitive development by 5 years of age, with potential implications for school performance. They are consistent with a recent finding in a parallel cohort in New York City, where Perera et al. (2009) found that after adjustment for maternal intelligence, quality of the home caretaking environment, environmental tobacco smoke exposure, and other potentially confounding factors. Children in the high-exposure group had full-scale and verbal IQ scores that were 4.31 and 4.67 points lower, respectively, than those of less-exposed children.

**DISINFECTANT BY-PRODUCTS (DBPs) & TRIHALOMETHANES (THMs)**

Disinfection of public drinking water supplies with chlorine or other disinfectants has been integral to the prevention of infectious waterborne diseases. The highly reactive nature of chlorine or other oxidants used as disinfectants, which aids in microbial inactivation, also causes them to form a number of disinfection by-products (DBPs) with naturally occurring organic and inorganic substances in the source water. Since the discovery of DBP formation in the mid-1970s, there has been increasing apprehension about the possible health effects posed by DBPs. Toxicological studies have shown that certain DBPs cause cancer in the liver, kidney and/or large intestine of laboratory animals and that particular DBPs cause adverse reproductive or developmental effects (Krasner, 2009).

Epidemiological studies have indicated a slightly increased risk for bladder, colon and rectal cancers in individuals who were exposed to chlorinated surface waters for many years. In addition, some epidemiology studies have shown an association between the consumption of chlorinated drinking water and adverse reproductive or developmental health effects, such as spontaneous abortion or fetal anomalies (Hoffman et al., 2008).

Exposures to drinking water disinfection by-products (DBP) during pregnancy may increase the risk of adverse pregnancy outcomes. Some studies report a moderately increased risk of delivering a small-for-gestational-age (SGA) infant among women exposed to high levels of total trihalomethanes (TTHMs), while other studies have shown exposure to high levels of TTHMs have been associated with decreased mean birth weight and an increased risk of delivering a low birth weight infant. Although they have been associated with having effects on fetal growth, these studies have not established a clear and consistent relationship (Hoffman et al., 2008).

Toxicologic data suggest that brominated THMs are likely to be more harmful to the fetus than chloroform. However, results of epidemiologic studies as a whole have not implicated any particular constituent of TTHM as being more or less harmful with respect to fetal growth. Hoffman et al. (008)’s study is the most extensive study of DBP exposure and fetal growth restriction conducted to date. The
results do not suggest an adverse effect of residential TTHM levels within the regulatory limits on fetal growth. In addition, none of the individual TTHM was consistently associated with fetal growth restriction (Hoffman et al., 2008).

Swimming pools constitute environments with high levels of DBPs in water and air due to continuous disinfection and constant organic load from bathers (e.g., urine, sweat, cosmetics, skin cells, and hair). One of the most prevalent DBPs in chlorinated swimming pools is THMs, with average concentrations ranging from 16 μg/L to 132 μg/L. Chronic exposure to DBPs through different routes has been associated with an increased risk for bladder cancer. Trichloramine and other volatile chemicals in swimming pools are respiratory irritants; pool attendance has been associated with asthma and other respiratory effects in Olympic swimmers and pool workers, and less clearly with recreational adult swimmers and children. However, the mechanisms are poorly understood, and it is not known with certainty whether trichloramine or other volatile pool DBPs are responsible. Despite the public health relevance, only a few studies, most rather recent, have investigated the chemistry and potential health effects of swimming pool water (Richardson et al., 2010).

Numerous epidemiological studies have been conducted to investigate the correlations between DBPs and several diseases. These studies have found that populations exposed to chlorination by-products have increased rates of bladder, colon–rectum, and brain cancers. In particular, human bladder cancer has been consistently linked with long-term exposure. These observations are supported by evidence of mutagenicity of the mixture and carcinogenicity of some constituents. To date, the role of genetic variability in modulating adverse health effects of DBPs has received limited attention, and bladder cancer has not been studied in this regard (Cantor et al., 2010).

Chlorine is a cost-effective drinking water disinfectant that has been used since the early twentieth century to control a panoply of waterborne infectious diseases. The by-products of the interaction of chlorine with organic precursors in water require further investigation in order to have a full characterization of the chemicals and its health effects.

PESTICIDES

The term “pesticide” covers a broad range of compounds used in pest control and includes insecticides, herbicides, fungicides, rodenticides, biologics, plant or insect growth regulators, nematocides, and nonspecific biocides. Since 1970, it has been estimated that approximately 2.8 billion kilograms of pesticide active ingredients was sold, representing 900 active ingredients and 50,000 commercial pesticide formulations. Although the benefits of pesticides are well-recognized their potential adverse effects on human health remain unclear (apart from acute poisonings, mainly involving insecticides). Studies show that a number of pesticides and pesticide combinations, including some still registered for use in Canada, can act as endocrine modulators, neurotoxicants, immunotoxicants, and carcinogens in animals and humans. Both animal and human studies suggested that the developing embryo is more vulnerable to the toxic effects of a number of environmental agents. During weeks 3 to 8 of fetal development, most of the major organs and body regions are being formed. Maternal exposure to teratogens during organogenesis is the best known causative pathway of producing birth defects. Before this time, insults are more likely to either kill the embryo or be compensated for by the potent regulatory properties of the early embryo. There is also growing
evidence to suggest that fetal and early life events can affect a person’s health later in life (Weselak et al., 2007).

Exposure to pesticides can occur directly from occupational, agricultural and household use, as well as indirectly through the diet. Over the past 2 decades there have been moves to replace organochlorine (OC) pesticides, which bioaccumulate in fatty tissue and persist in the environment for decades, with organophosphate pesticides (OP) and other chemicals which are shorter lived. However, OPs still possess significant toxicity. In the past few decades hundreds of studies have attempted to establish whether chronic pesticide exposure has adverse effects. A recent systematic review examined the literature on the human health effects of currently used pesticides (OCs were excluded). The review found a high level of consistency across multiple studies indicating a wide range of pesticide related clinical and subclinical effects including significant positive associations between pesticide exposure and solid tumours, haematological cancers and genotoxic effects. In addition, pesticides were found to impact on mental and emotional functioning, the nervous system (causing neurodegenerative disease) and the reproductive system (causing birth defects, fertility, fetal death, and intrauterine growth retardation) (Sanborn et al., 2007).

Pesticides were also reviewed in 2004 by the Ontario College of Family Physicians, covering studies conducted since 1992. The evidence linked pesticide exposure, from both occupational and residential use, with many serious illnesses including cancer, reproductive and development problems, and neurological diseases. The overall message emanating from the review was that no safe level of exposure is discernible from the evidence and that exposure to pesticides should be avoided with special concern for children (Sanborn et al., 2007). Many of the organochlorine (e.g., DDT), organophosphate and carbamate insecticides have been banned because of their toxicity and persistence in the environment. Thus, exposure to chlordane, dieldrin, heptachlor, toxaphene, and HCB are thought to be minimal because of their restricted use. Methoxychlor, Vinclozolin, and Atrazine remain registered pesticides in use in Canada, whereas a number of European countries instituted bans on them in the 1990s (Weselak et al., 2007).

Pesticides are toxic in humans in their ability to inhibit cholinesterase which can over stimulate the nervous system and result in nausea, dizziness, confusion and, in the case of accidents or major spills (very high exposures), respiratory paralysis and death may result. Prenatal exposure to pesticides has been associated with an increased risk of spontaneous abortion, birth defects, brain tumours, fetal death and early childhood cancers such as acute lymphocytic leukemia (Weselak et al., 2007).

Beginning in the 1990s, a series of reports demonstrated that consumption of PCB-contaminated Great Lakes fish resulted in altered birth weight, growth, and development in children. Weisskopf et al. (2005) reported that Great Lakes sport-caught fish (GLSCF) consuming mothers had higher serum PCB and DDE concentrations, but only increased DDE was associated with lower birth weight. Overall, the data suggests that fetal DDE exposure may decrease birth weight and that decreased birth weight effects associated with GLSCF consumption have decreased over time (Weisskopf et al., 2005). But recent studies challenge the relationship between maternal pesticide use/exposure and low birth weight (see Sathyanarayana et al., 2010). Neurobehavioral deficits have been demonstrated in some children prenatally exposed to pesticides (see Harari et al., 2010). Organochlorine pesticides have also been associated with attention deficit hyperactivity disorder (Sagiv et al., 2010).
In adults, agricultural exposure to pesticides has been recently associated with heart disease, especially non-fatal myocardial infarction in the U.S. Pesticide exposure has also been related to cancer risk. Bassil et al. (2007) systematically reviewed the association of pesticide and cancer and found most studies on non-Hodgkin lymphoma and leukemia showed positive associations with pesticide exposure. Some showed dose-response relationships, and a few were able to identify specific pesticides.

Children's and pregnant women's exposure to pesticides was positively associated with the cancers investigated in some studies, as was parents' exposure to pesticides at work. Many studies showed positive associations between pesticide exposure and solid tumours. The most consistent associations were found for brain and prostate cancer. An association was also found between kidney cancer in children and their parents' exposure to pesticides at work. These associations were most consistent for high and prolonged exposures. Specific weaknesses and inherent limitations in epidemiologic studies were noted, particularly around ascertaining whether and how much exposure had taken place. Weichenthal et al. (2010) reviewed 28 studies; most of the 32 pesticides examined were not strongly associated with cancer incidence in pesticide applicators. Increased rate ratios (or odds ratios) and positive exposure-response patterns were reported for 12 pesticides currently registered in Canada and/or the United States (alachlor, aldicarb, carbaryl, chlorpyrifos, diazinon, dicamba, S-ethyl-N,N-dipropylthiocarbamate, imazethapyr, metolachlor, pendimethalin, permethrin, trifluralin). However, estimates of association for specific cancers were often imprecise because of small numbers of exposed cases, and clear monotonic exposure-response patterns were not always apparent. Exposure misclassification is also a concern in the agricultural health study and may limit the analysis of exposure-response patterns. Epidemiologic evidence outside the agricultural health study remains limited with respect to most of the observed associations, but animal toxicity data support the biological plausibility of relationships observed for alachlor, carbaryl, metolachlor, pendimethalin, permethrin, and trifluralin (Weichenthal et al., 2010).

Pesticides may also have non-cancer end points. Strong evidence of association with pesticide exposure was found for neurologic outcomes, genotoxicity, and 4 of 6 reproductive effects: birth defects, fetal death, altered growth, and other outcomes. Exposure to pesticides generally doubled the level of genetic damage as measured by chromosome aberrations in lymphocytes. Only a few high-quality studies focused on the dermatologic effects of pesticides. In some of these studies, rates of dermatitis were higher among those who had had high exposure to pesticides on the job (Sanborn et al., 2007).

Specific neurotoxic evidence has grown from results of various studies pointing to a possible link between pesticides and Parkinson’s disease (PD) which is an idiopathic disease of the nervous system characterized by progressive tremor, bradykinesia, rigidity, and postural instability. It has been postulated that exogenous toxicants, including pesticides, might be involved in the etiology of PD. Brown et al. (2006) review the published epidemiologic and toxicologic literature and critically evaluate whether a relationship exists between pesticide exposure and PD. From the epidemiologic literature, there does appear to be a relatively consistent relationship between pesticide exposure and PD. This relationship appears strongest for exposure to herbicides and insecticides, and after long durations of exposure. Toxicologic data suggest that paraquat and rotenone may have neurotoxic actions that potentially play a role in the development of PD, with limited data for other pesticides.
However, both the epidemiology and toxicology studies were limited by methodologic weaknesses. Particular issues of current and future interest include multiple exposures (both pesticides and other exogenous toxicants), developmental exposures, and gene-environment interactions. At present, the weight of evidence is sufficient to conclude that a generic association between pesticide exposure and PD exists but is insufficient for concluding that this is a causal relationship or that such a relationship exists for any particular pesticide compound or combined pesticide and other exogenous toxicant exposure (Brown et al., 2006).

Other factors are likely involved. A study by Sanyal et al. (2010) revealed that family history of PD, pesticide exposure, exposure to toxins other than pesticides and herbicides, rural living and previous history of depression were associated with increased risk of PD, whereas smoking appeared to be a protective factor. Well water drinking for at least five years, though a significant risk factor, could not be proved significant in multivariate analysis. Head trauma, vegetarian dietary habit, occupation involving physical exertion and exposure to domestic pets were not significant risk factors.

ENGINEERED NANOTECHNOLOGY

Nanoparticles/materials are generally defined as materials that are <100 nm (0.1 μm) in at least one dimension. This means that nanoparticles/materials can be three-dimensional particles of almost any shape, ultrathin films (two-dimensional-like), or fine rods (essentially one-dimensional). The growth of engineered nanotechnology is staggering; it currently represents a greater than $100 billion dollar global industry, with some analysts predicting that global revenues from engineered nanotechnology-enabled products to be worth $2 to 3 trillion by 2015. More than 1000 products that contain manufactured nanotechnologies are currently commercially available in various industries (Bernhardt et al., 2010) such as electronics, healthcare, chemicals, cosmetics, materials and energy and function in these industries to create lighter and stronger materials, to clean contaminated environment, for replacing toxic chemicals in various applications, for enhancing solar cell efficiency, and for targeted cancer treatment (Kahru and Savolainen, 2010), with thousands more applications in development including for use as pesticides and fertilizers in agriculture (Unrine et al., 2010). The size of a nanoparticle affects its properties and, by extension, its environmental/biological behaviour: chemical (reactivity, solubility, etc.), mechanical (elasticity, hardness, etc.), electronic (conductivity, redox behavior, etc.), and nuclear (magnetic) properties often change as a function of size. These changes can be, and often are, dramatic. This is precisely what leads to the exceptional commercial value of manufactured nanotechnologies. There exists, however, an exceptionally wide variety of naturally occurring nanoparticles in both biotic and abiotic organisms. The most abundant of these particles include ash from volcanoes and forest fires, sea salt aerosols, and the iron and other transition metal oxides in soils, rivers, and oceans (Bernhardt et al., 2010).

Despite extensive research on potential applications of engineered nanotechnology in recent years, comparatively little has been done to evaluate their potential environmental hazards, particularly in terrestrial ecosystems. It is particularly important to consider food chain accumulation of anthropologic nanomaterials in agroecosystems because diet via the consumption of grain crops and meat products is a key exposure pathway for humans and other ecological receptor species. Furthermore, it has been shown that some engineered metal nanomaterials can be absorbed gastrointestinally and penetrate cell membranes in animals and can be taken up by plants.
Earthworms can accumulate copper ions and manufactured oxidized copper nanoparticles from soil, suggesting a route of entry for anthropologic copper-based nanoparticles into terrestrial food chains (Unrine et al., 2010).

Animal experiments have shown that manufactured nanotechnologies (metallic nanoparticles, quantum dots, carbon nanotubes) can translocate to the brain from different entry points (skin, blood, respiratory pathways). After inhalation or instillation into parts of the respiratory tract a very small fraction of the inhaled or instilled anthropologic nanoparticle reaches the blood and subsequently secondary organs, including the central nervous system, at a low translocation rate. Experimental in vivo and in vitro studies have shown that several types of manufactured nanotechnologies can have various biological effects in the nervous system. Some of these effects could also imply that engineered nanotechnologies can cause hazards, both acutely and in the long term. The relevance of these data for risk assessment is far from clear. There are at present very few data on exposure of the general public to either acute high dose exposure or on chronic exposure to low levels of air-borne manufactured nanotechnologies (Simkó and Mattsson, 2010).

The situation is more complicated regarding chronic exposures, at low doses. The long term accumulation of anthropologic nanotechnologies cannot be excluded. Exposure data for the general public regarding manufactured nanotechnologies does not exist. It is known that translocation to the brain via respiratory organs and the circulatory system is very low, even in cases where engineered nanotechnologies have such surface modifications as to be able pass through the blood-brain barrier. At higher concentrations, it is biologically plausible, however, that an engineered nanoparticle/material can enter the olfactory bulb via the olfactory nerve, and then potentially distribute to other areas of the brain. Similarly, a possibility remains that chronic exposures, and/or biopersistent manufactured nanotechnologies can influence processes within the brain that trigger or aggravate other pathological processes. In general, the present state of knowledge is unsatisfactory for a proper risk assessment in this area. Crucial deficits include lack of exposure data, the absence of a proper dose concept, and that studies often fail in providing an adequate description of the investigated engineered nanotechnology (Simkó and Mattsson, 2010).
EMERGING CHEMICALS OF CONCERN

PERSONAL CARE PRODUCTS & PHARMACEUTICALS

Personal Care Products

In recent years, studies have been conducted to determine whether components of personal care products (e.g., cosmetics, soaps, hair sprays, lotions, nail polishes, shampoos etc.) exhibit endocrine disruptor activity and, if so, whether evidence exists that they adversely affect consumers of these products. With respect to possible endocrine disrupting properties and subsequent health effects in humans, the primary constituents under examination in current research literature are phthalate esters, parabens, ultraviolet (UV) filters, synthetic polycyclic musks, and antimicrobials (Witorsch and Thomas, 2010).

Phthalates

A study by Hubinger and Havery (2006) suggest that the amount of phthalate exposure from personal care products is small relative to other sources of exposure. For example, phthalate absorption from nail polish through the nail is minimized because this product dries rapidly. Since soaps, shampoos,
and conditioners are washed off the skin, phthalate exposure through this route would also be short-lived. Hubinger and Havery (2006) further suggest that phthalate exposure from products that are left on the skin (i.e., lotions and creams) is slow, due to the fact that the rate of phthalate absorption in human skin is slow (Witorsch and Thomas, 2010).

According to a review by Witorsch and Thomas (2010) in utero exposure of male rats to high doses (in excess of 100 mg/kg/day) of certain phthalate esters (i.e., those esterified to longer alkyl groups) exhibit a battery of demasculinizing characteristics. Some of these characteristics are reminiscent of a condition in humans referred to as “testicular dysgenesis syndrome” (TDS). At least two mechanisms may account for testicular dysgenesis-like characteristics, impairment of testosterone production by the fetal testes or interference with testosterone action at its target tissue, either occurring at critical stages of development. In the case of phthalate effects in the rat, the mechanism is clearly defined, i.e., impaired testosterone production by the fetal testes. The etiology of TDS in humans is yet undefined. Witorsch and Thomas (2010) conclude the unlikelihood that phthalate exposure is a cause of TDS. The amounts of phthalates required to produce demasculinizing effects in rats are very high, several orders of magnitude higher than humans would be exposed to on a daily basis.

**Parabens**

As a result of their bactericidal or fungicidal properties, parabens have been used as preservatives for pharmaceuticals, cosmetics, toiletries, and foods for more than 80 years. The chain length of the alkyl group on the paraben is directly proportional to their antimicrobial activity and inversely related to their water solubility. Parabens, as a group, exhibit very weak estrogenic activity both in vitro and in vivo. Although estrogen-related actions of selected parabens have been reported in vitro, such as inhibition of aromatase activity, it is unlikely that they are of significance in vivo because of the high concentration of paraben required to produce such effects. Further, no consistent evidence exists that parabens produce toxic effects in developing or neonatal rats. And no convincing data exist that parabens produce adverse effects in humans. Whereas parabens have been detected in human breast cancer specimens, the study lacked estimates of parabens in normal breast tissue and the levels detected were actually several orders of magnitude lower than those required to produce estrogenic effects. Furthermore, the one published functional study in humans has failed to demonstrate that parabens affect endocrine/reproductive endpoints (Witorsch and Thomas, 2010).

**UV Filters**

UV filters are a diverse array of lipophilic chemicals capable of absorbing either UVA (400 to 320 nm) or UVB (320 to 280 nm) radiation, ideal for use as sunscreens. They are also included in cosmetics such as skin lotions, beauty creams, lipsticks, and hairsprays for purposes of prolonging the shelf-life of these products. Some UV filters possess estrogenic activity both in vitro and in vivo, however, this activity is very weak and requires very high doses to manifest in vivo. A series of multi-generational rodent studies reported isolated effects of two chemically related UV filters, 4-MBC and 3-BC. In general, the effects observed were sporadic and lack a plausible physiological mechanism. Several multi-organ studies examining traditional and gene-expression endpoints have revealed that high doses of select UV-filters produce effects, some of which mimic the action of estrogen and some of which are actually nonestrogenic. High doses of 4-MBC and BP-2 in rats appear to evoke goitrogenic
antithyroid effects in vivo. To date, no human data exist to suggest that UV filters evoke endocrine disruptive effects (Witorsch and Thomas, 2010).

A recent study by Schlumpf et al. (2010) found frequently used UV filters in a large proportion of human milk samples, at concentrations comparable to PCBs. Comparison with a detailed questionnaire revealed that the presence of UV filters in human milk was closely linked with the use of cosmetics containing these chemicals, indicating that internal exposure resulted from repeated application of cosmetics rather than from general environmental exposure. Another absorption study in humans indicated that topically applied select UV filters penetrate the skin and appear within blood (Witorsch and Thomas, 2010).

Anti-Microbials

Triclocarban (TCC) and triclosan (TCS) are widely used antimicrobial (antibacterial and/or antifungal) agents in personal care products. These two compounds are contained in approximately 45% of commercial liquid and bar soaps. In addition, antimicrobials are found in mouthwash, toothpaste, cosmetics, fabrics, plastics, and pharmaceuticals. Recently there has been increased interest as to whether the antimicrobials TCS and TCC exhibit endocrine disruptor activity. Among the areas that have been examined are interactions with the aryl hydrocarbon receptor (AhR), estrogen receptor (ER), and androgen receptor (AR), as well as effects on the thyroid system. TCC exhibits weak estrogen agonist activity and appears to amplify the actions of estrogens at the ER. It is not known whether this modest amplification is additive or synergistic. There also exists a positive interaction between TCC and testosterone suggesting a novel relationship between an environmental chemical, endogenous hormone, and hormone receptor, and requires further examination. TCS has been shown to have anti-androgenic effect in cell-based bioassays which, thus far, is not evident in vivo (Witorsch and Thomas, 2010). In a recently published critical review of the experimental toxicology and risk analysis literature pertaining to TCS, Rodricks et al. (2010) conclude that this substance in consumer products does not appear to cause adverse health effects in people.

Pharmaceuticals

With respect to future long-term exposure, pharmaceuticals may be relevant. They are often excreted unchanged and can reach the environment. Throughout developed countries, the pharmaceutical concentrations in the aquatic environment are in the same range (μg L−1 and below); however, it is not clear whether this holds for less-developed countries too. The health risks of active pharmaceutical ingredients (APIs) remain poorly understood. Although there are no known short term effects on humans, long-term effects cannot be ruled out until there is more research. The significance of metabolites and transformation products resulting from the parent APIs is not yet known. Awareness of the presence of pharmaceuticals in the environment, coupled with some evidence of effects, suggests that precautionary management action to reduce the release of pharmaceuticals to the environment should be considered. As for effluent treatment, no technology works well for all compounds. Kummerer (2010) goes on to note that the risks posed to humans from pharmaceuticals in the environment seem to concern environmental hygiene rather than toxicology and pharmacology. However, there are some exceptions: Endocrine-active compounds and hormones may interfere with sexual development in humans, as they are highly active compounds that interact
with hormone systems. In addition, some anticancer drugs may cause cancer themselves—even at very low doses—one of the threats of modern chemotherapy, and antibiotics may contribute to the selection of bacteria that are resistant against antibiotics. Little knowledge of these issues is available. The maximum possible intake with contaminated water within a life span (2 liters drinking water per day over 70 years) is far below the dosages used in general therapy. However, this statement relies on some assumptions: (a) that the effects and side effects during therapeutic use (short-term, high dosage) are the same in quality and quantity as during a lifelong ingestion (long-term ingestion, low dosage); (b) that the effects are the same for fetuses, babies, children, healthy adults, and elderly people; (c) and that the risk imposed by a single compound is comparable to the one imposed by a mixture. How to extrapolate data from high-dose short term ingestion during therapy to a low-dose long-term ingestion, i.e., medication received via drinking water, is still an unresolved issue in toxicology and in ecotoxicology. Elderly people, little children, and pregnant women may be at risk; however, they are often not specifically addressed in risk assessments. Information about the effects of the active substances on organisms in the aquatic and terrestrial environments is increasing but still too little. Effects on fish, daphnia, algae, and bacteria have been demonstrated using low concentrations in long-term tests. For diclofenac, the effective concentration for chronic fish toxicity was in the range of wastewater concentrations, whereas those of propranolol and fluoxetine for zooplankton and benthic organisms were near the maximally measured STP effluent concentrations. In surface water, concentrations are lower and so are the environmental risks. However, targeted ecotoxicological studies are almost entirely lacking, and such investigations are needed to focus on subtle environmental effects. Chronic effects often do not have clearly visible results. Instead, they may cause subtle changes within longer time spans. Therefore, such effects are often overlooked, and a direct cause-and-effect relationship cannot be established on an ecosystem level.

CHLORINATED PARAFFINS

Chlorinated paraffins (CPs) are industrial chemicals widely used as additives in metal working fluids, flame retardants in rubbers, additives in paints, coatings, sealants and adhesives, and have been in production since the 1930s. CPs are comprised of chlorinated straight chain hydrocarbons which can reach a length of 30 carbons with a chlorine content usually between 30-70% (Magalihoude et al., 2008). As such, they can be subdivided into three main groups according to the length of the chain: short (C_{10–13})(SCCP), medium (C_{14–17})(MCCP) and long (C_{>17})(LCCP)(Bezchlebová et al., 2007). Having similar physical and chemical properties to other persistent organic pollutants (e.g., PCBs, DDT)(Feo et al., 2009) CPs replaced PCBs in the mid-1980s. SCCPs have been placed on the U.S. EPA’s Toxics Release Inventory and are on the First Priority Substances List under the Canadian Environmental Protection Act. In the 1990s, annual world-wide production of chlorinated paraffins was estimated to be 300 kilotons (Magalihoude et al., 2008), with the United States producing 100 million pounds in 2007 (EPA, 2009); CPs are no longer produced in Canada (Environment Canada, 2010b). The environmental release of CPs may occur during the production, storage, transportation, and use of CP-based products or during leaching, runoff, or volatilization from landfill, sewage sludge, waste disposal sites, and incineration. SCCPs have the highest potential for environmental release because of open use (e.g., metal working fluids) (Magalihoude et al., 2008). CPs exert a high potential for bioaccumulation, with strong sorption on sewage sludge, soils and sediments and very low mobility (Bezchlebová et al., 2007).
A study of SCCPs and MCCPs in the food web in Lake Ontario and Michigan revealed these flame retardant chemicals are widely distributed in water and biota samples. The relatively high concentrations of SCCPs and MCCPs detected in deepwater and slimy sculpin from Lake Michigan and Ontario, respectively, suggest that sediment may be a source of contamination for these bottom-dwelling fish. Sources and pathways of SCCP/MCCPs may differ due to different industrial and consumer use, particularly for MCCPs, which are incorporated as flame retardant plasticizers into many products. MCCPs, which are more hydrophobic and less volatile than SCCPs, may show more distinct gradients from urban source areas. Results illustrated that the proportion of MCCPs differed greatly between the two lakes with MCCPs much more prominent in Lake Ontario and elevated concentrations of SCCPs were observed in fish near industrial areas in the Great Lakes. The authors suggest that given the prominence of CPs, particularly in lake waters and in lower food web organisms, further investigation is needed to evaluate the magnitude of the distribution and accumulation/magnification of SCCP/MCCPs (Magalihoude et al., 2008).

On the whole, information on environmental levels of CPs is scarce as compared to that for other persistent organic pollutants (e.g., PCBs, dioxins, and organochlorine pesticides). The main reason is the demanding nature of analysis of CPs in environmental matrices due to their complex composition. Thus far, most environmental information is on SCCPs, with very little on MCCPs, and a dearth of information on environmental levels on LCCPs (Feo et al, 2009).

Similarly, the amount of toxicological data on CPs is limited, the majority data having been produced using commercial CP formulations. This presents challenges as CP products comprise thousand of compounds, so differences in the toxicity of individual components cannot be easily identified. Because of the selective degradation, biodegradation, biotransformation, and bioaccumulation of individual CP compounds in the environment, the relative abundance of individual CP compounds to which an organism is exposed may vary from the proportions in the original CP product. The lack of appropriate analytical techniques has also resulted in uncertain estimates of exposure concentrations and body burdens. Of known toxicological effects, SCCPs are generally more pronounced than those of MCCPs and LCCPs. SCCPs have shown carcinogenic potential in rats and mice, while no evidence of carcinogenicity was found for MCCPs and LCCPs (Feo et al., 2009).

In Canada, Environment Canada has concluded that short, medium, and certain long chain CPs are toxic to the environment, as defined under Canadian Environmental Protection Act, 1999 (CEPA 1999), and would be proposed as candidates for virtual elimination. Further, Health Canada also has concluded that short chain CPs are toxic to human health and proposes that medium and long chain CPs are suspected to be toxic to human health (Environment Canada, 2008).

In the United States, the National Cancer Institute lists chlorinated paraffins (C12, 60 percent chlorine) as reasonably anticipated to be human carcinogens based on sufficient evidence of carcinogenicity in experimental animals. They are classified by the IARC as Group 2B - possibly carcinogenic to humans based on sufficient evidence of carcinogenicity in experimental animals and mechanistic considerations. According to the EPA’s website, “[t]here is no experimental evidence using human data that demonstrates the carcinogenicity of SCCPs” (EPA, 2009).

In conducting its review of CPs, the EPA determined that some of the specific CPs currently being manufactured and/or used in the United States are not on the Toxic Substances Control Act (TSCA)
Inventory. The EPA intends to initiate action under TSCA section 6(a) to ban or restrict the manufacture, import, processing or distribution in commerce, export, and use of SCCPs based on the persistence, bioaccumulation and toxicity of SCCPs and their presence in the environment. The EPA intends to further evaluate whether the manufacturing, processing, distribution in commerce, use and/or disposal of MCCPs and LCCPs should also be addressed under TSCA section 6(a)(EPA, 2010a).

Figure 7. CPA [CP] levels in Different Environmental Compartments as well as biota and human matrices.


SYNTHETIC MUSKS

Nitro musk compounds were first synthesized at the end of the 19th century as fragrance substitutes for natural musk obtained from musk pods of the endangered male musk deer. In the 1950s and 1960s, polycyclic musk compounds were developed. These synthetic musk compounds have been extensively used as fragrance ingredients in consumer products such as cosmetics, detergents, fabric softeners, shampoos, perfumes and other scented personal care products (Lee et al., 2010). Worldwide, synthetic musks are commercially produced in the thousands of tons per year (EPA, 2011). The detection of nitro and polycyclic musks in human and environmental samples (e.g., sewage sludge, air, wastewater, sediment, fish, and human tissues and milk) in addition to their carcinogenic properties initiated a public debate on the use of these compounds and a ban or reduction of their use (especially for nitro musks) in many regions of the world, including Japan, Germany and China (Hu et al., 2010). Over the past few decades use of polycyclic musks has been increasing (Lee et al., 2010). It is expected that in the future macrocyclic musk compounds are expected to replace both nitro and polycyclic musks since these compounds appear to be safer (Sommer, 2004). Synthetic musks are so extensively used that they found in sewage aeration basins producing substantial atmospheric emissions of these compounds (Upadhyay et al., 2011) in addition to partitioning to sewage sludge due to their solubility in fat (EPA, 2011).
Polycyclic musks, although interacting with estrogen receptor, and androgen receptor or progesterone receptor, appear to exhibit only antagonist activity and no agonist activity in vitro. These effects, however, are usually weak. For the most part, hormonal or anti-hormonal activity of polycyclic musks has yet to be confirmed in vivo. Although antiestrogenic activity of select polycyclic musks has been observed in zebrafish, this aquatic environment differs substantially from human exposure to fragrances in personal care products (Witorsch and Thomas, 2010). Few studies have been undertaken examining the presence of synthetic musks in humans. Of those recently published (2008-2010), the findings have indicated that use of personal care products, especially perfumes and body lotions, is the primary source of entry into the body (Hutter et al., 2009; 2010). Levels of nitro musk in human milk have been shown to be dropping while levels of polycyclic musks in milk have been increasing with one study finding the presence of one compound of macrocyclic musk in human milk (Schlumpf et al., 2010; Lignell et al., 2008). Similarly, synthetic musks found in human blood show the decline in the presence of nitro musk and increase in the presence of polycyclic musks (Hu et al, 2010). At this point, there are no known health effects associated with synthetic musks.

**PHTHALATES**

Phthalates (or phthalate esters) are dialkyl or alkyl aryl esters of phthalic acid. Phthalates were first produced in the 1920s, with large-scale commercial production being introduced during the 1950s when polyvinyl chloride (PVC) (which is softened by phthalate esters) was first developed. Phthalates are used in a wide variety of products and applications including, gelling agents, medical devices, cosmetics, adhesives, lubricants, dispersants, emulsifying agents, household PVC interior surface coverings (i.e., floors, tiles), shower curtains, food wrappings, nail polish, plastic goods and kitchen plasticware. The most widely used phthalates have been di-2-ethylhexyl phthalate (DEHP), with lesser used phthalates including butyl benzyl phthalate (BBP), diisobutyl phthalate (DIBP) and diethylphthalate (DEP). Recently longer chain phthalates such as diisodecyl phthalate (DIDP), diisononyl phthalate (DINP), or di-2-propylheptyl phthalate (DPHP) are increasingly being used in place of DEHP (Kimber and Dearman, 2010). Phthalates and their metabolites are also divided into molecular weight: low (e.g., DEP, DBP) and high (e.g., DEHP).

Diet is the largest source of human exposure to phthalates. In one study of foodstuffs, poultry consumption was significantly associated with DEHP metabolites; egg consumption was significantly associated with levels of MEP (metabolite of DEP) suggesting that chickens themselves may be contaminated with phthalates, and that chicken meat is not solely contaminated through packaging and processing; fruit and vegetable consumption was associated with metabolites of DEP and DMP; and meat intake was associated with the metabolite of DEP, but not with DEHP metabolites as poultry was. The authors suggest this last finding illustrates a potentially different source of contamination in poultry compared with meat (Colacino et al., 2010).

The highest levels of exposure (for individuals) derive from the use of DEHP in medical plastics and thus the intravenous route is of importance for those patients undergoing renal dialysis or blood transfusions; other exposure routes to phthalates include inhalation and dermal. Previously, infant exposure may have derived from the use of childcare products and plastic toys. However, since 1999,
the use of three phthalate esters (DEHP, DBP and BBP) in such articles has been banned completely in the European Union and three others (DNIP, DIDP and di-n-octyl phthalate [DNOP]) are banned from use in the same applications where the articles may be put into the mouth of a child. Since 2008, a similar restriction has been in place in the U.S. (Kimber and Dearman, 2010). In 2011, Health Canada announced new regulations that restricts the allowable concentrations of DEHP, DBP, BBP, DINP, DIDP and DNOP in children's toys and child care articles where the soft vinyl can, in a reasonably foreseeable manner, be placed in the mouth of a child under 48 months of age (Health Canada, 2011).

Phthalates are ubiquitous in both the environment and in humans. The CDC, as part of the National Health and Nutrition Examination Survey (NHANES), has consistently found urinary concentrations of phthalates in a representative sample of the U.S. general population aged 6 years and older. Phthalates have been classified as endocrine disruptors, hormonally active compounds linked to reproductive toxicity in both animals and humans. These compounds also exhibit anti-androgenic or weakly estrogenic activity, adversely impacting thyroid hormone regulation (Miodovnik et al., 2011). One recent study of children aged 4-9 years found that thyroid hormones may have an accelerating effect on the metabolism of phthalates. Finding also included an association between phthalate exposure and growth which supports the conclusion that phthalate exposure in this age group exerts an adverse biological effect as thyroid hormones and growth factors are closely linked with each other and contribute significantly in the regulation of childhood growth (Boas et al., 2010).

Recent studies have examined other possible health effects, with many requiring replication of study results as they are new areas of investigation. One such study examined the behaviour profiles of children clinically diagnosed with disruptive behaviour disorders, for example, oppositional defiant disorder, conduct disorder, or ADHD and found an association with prenatal (third trimester) low molecular-weight metabolite concentrations in maternal urine. The mechanism underlying a possible association between phthalates and neurodevelopment has not been established, but may include prenatal disruption of the maternal thyroid hormone system or activation of peroxisome proliferator-activated receptors, a biologically plausible explanation for the study's findings (Engel et al., 2010). Two recent studies investigated phthalates and asthma, one in children and one in adults. Both studies found some of the early key mechanisms in the pathology of allergic asthma could possibly be targeted by phthalate exposure (Bornehag and Nanberg, 2010) but no causal relationship between phthalates and asthma has been established to the exclusion of other exposures, and that demonstration of dose-related correlations between phthalate exposure and respiratory symptoms has proven elusive (Kimber and Dearman, 2010). Lastly, a study of breast cancer and nine phthalate metabolites found that that exposure to diethyl phthalate (DEP), the parent compound of MEP, may be associated with increased risk of breast cancer, whereas exposure to the parent phthalates of MBzP and MCPP might be negatively associated (Lopez-Carillo et al., 2010).

**ALKYLPHENOL ETHOXYLATES**

Alkylphenol ethoxylates are the most widely used classes of non-ionic surfactants in industrial, agricultural and household applications. Various plastic food containers and wrappings have been found to allow migration of alkylphenols residue into foodstuffs. Some 60% of used alkylphenol ethoxylates are discharged (Ferrara et al., 2011) into the aquatic environment via industrial effluents, municipal wastewater treatment plant effluents (i.e., liquid and sludge) and direct discharge (Health
Canada and Environment Canada, 2001) where they are degraded to shorter-chain and more persistent alkylphenols such as nonylphenol (NP) and octylphenol (Ferarra et al., 2011). NP is persistent in the aquatic environment, moderately bioaccumulative, and extremely toxic to aquatic organisms. The main use of NPs is in the manufacture of NPEs. NPEs are non-ionic surfactants that are used in a wide variety of industrial applications and consumer products. NPEs, though less toxic than NP, are also highly toxic to aquatic organisms, and in the environment degrade to more environmentally persistent NP (EPA, 2010b). NPEs represent approximately 80% of alkylphenol ethoxylates, with octylphenol ethoxylates as the remaining 20% (Ferarra et al., 2011). NPEs are high-volume chemicals that have been used for more than 40 years as detergents, emulsifiers, wetting agents and dispersing agents (Health Canada and Environment Canada, 2001).

Alkylphenols ethoxylates (including NP and NPE) are considered weak estrogens as they do interact with estrogen receptors (Ferrara et al., 2011). Human exposure is a result of the presence of NP and NPEs in detergents, cleaners, agricultural and indoor pesticides, food packaging and cosmetics (EPA, 2010b). Direct exposures include the use of personal care products and detergents, and the use of spermicides in contraceptives (Ferarra et al., 2011). NP has been found in human blood, urine, adipose tissue, umbilical cord blood and breast milk (Ferarra et al., 2011; EPA, 2010b).

The U.S. EPA has recently released a “Nonylphenol (NP) and Nonylphenol Ethoxylates (NPEs) Action Plan”. NPs and NPEs are not listed in the Toxic Release Inventory ( TRI), however (EPA, 2010b). In Canada, NP and NPE are considered “toxic” under the Canadian Environmental Protection Act. They are not, however, considered a priority for investigation of options to reduce human exposure through control of sources that are addressed under CEPA 1999 (Health Canada, 2007).

**EMERGING HEALTH OUTCOMES OF CONCERN**

Thus far our report has focused on specific chemicals of concern in Ontario and the Great Lakes basin. Yet literatures are emerging on specific health outcomes linked to one or more pollutants. We review some of these outcomes.

**Synergistic Effects**

In general, understanding of the health impacts of chemical exposures is limited and often confined to single chemicals. In reality, our daily exposure profiles and the body burden consist of many chemicals. Little is known about the interaction effects or cumulative toxicity of two or twenty chemicals acting together in a mixture. One of the few standardized methods that have addressed the mixture issue is the development of the toxic equivalent factors (TEFs), which account for the fact that dioxins, furans and dioxin-like PCBs exhibit similar biochemical activities and toxicity (Carpenter et al., 2002). Mixtures can have additive, antagonistic, or synergistic effects in the body. Of special concern for human health are the instances of chemical synergy, wherein the mixture’s toxicity is greater than the sum of the individual toxicities of the components combined.

Synergy is a combined effect of two chemicals, which produces an effect potentially much larger than their additive effects. The most established and classic example of chemical synergism and the
consequent health impacts of this interaction is the relationship between asbestos exposure and cigarette smoking. Since smokers are ten times more likely to develop lung cancer than non-smokers, and individuals exposed to asbestos are at five times the risk of lung cancer compared to those not exposed, it might be expected that the combined risk would make these individuals 15 times more likely of developing lung cancer. But, the synergism between these two exposures increases the risk of developing lung cancer 80 times that of non-smokers not exposed to asbestos (Carpenter et al., 2002). Synergistic effects have also been found among chemical and social environmental factors in an uncertain aetiology. Correcting for potential confounders, Clougherty et al. (2007) found an elevated risk of asthma with a one standard deviation (4.3 ppb) increase in NO₂ exposure solely among children with above-median exposure to violence. Among children always living in the same community, with lesser exposure measurement error, this association was magnified. Of multiple exposure periods, year-of-diagnosis NO₂ was most predictive of asthma outcomes. The authors note then an association between traffic-related air pollution and asthma solely among urban children exposed to violence.

Animal studies show that diesel exhaust particles and oxidized phospholipids synergistically affect the genetic level through expression profile of several gene modules that correspond to pathways relevant to vascular inflammatory processes such as atherosclerosis. Kelly et al. (2010) investigated the independent and combined effects of exposure to the common herbicide glyphosate and a trematode parasite on survival and the development of spinal malformations a juvenile New Zealand freshwater fish species. Survival of juvenile fish was unaffected by exposure to glyphosate alone (at an environmentally relevant concentration) or by infection alone. However, simultaneous exposure to infection and glyphosate significantly reduced fish survival.

The ATSDR Chemical Mixtures Program has ensured interest in interaction profiles for chemical mixtures. Mauderly and Samet (2009) clarify the nature of potential interactions among pollutants. These are:

- **Additivity**: effect of the combination equals the sum of individual effects.
- **Synergism**: effect of the combination is greater than the sum of individual effects.
- **Antagonism**: effect of the combination is less than the sum of individual effects.
- **Inhibition**: a component having no effect reduces the effect of another component.
- **Potentiation**: a component having no effect increases the effect of another component.
- **Masking**: two components have opposite, cancelling effects such that no effect is observed from the combination.

“Effect” is taken to mean the observed expression of the particular health outcome in question. A combination of pollutants could have different interactions for different outcomes. The interaction could occur at any level of biological pathway from exposure to expression of the outcome. In 2004, ATSDR commented on its research program for chemical mixtures that includes trend analysis to identify the mixtures most often found in environmental media, in vivo and in vitro toxicological testing of mixtures, quantitative modeling of joint action, and methodological development. By 2010, the ATSDR developed 11 interaction profiles for chemicals of concern (for details see: [http://www.atsdr.cdc.gov/mixtures.html#bookmark04](http://www.atsdr.cdc.gov/mixtures.html#bookmark04)). Two of the ATSDR’s profiles consist of a mixture of persistent environmental contaminants commonly found in fish and breast milk, important
exposure pathways for many, including infants who are highly susceptible and sensitive to toxicant exposures. The mixtures consisted of the following chemicals: TCDD, hexachlorobenzene (HCB), DDE, methylmercury, and PCBs. The strongest associations were found between methylmercury and PCBs, and between HCB and TCDD. Specifically, synergistic effects were found in both directions for methylmercury and PCBs in disrupting the regulatory capacity of dopamine levels, which may influence neurological development (ATSDR, 2010). This finding supports earlier findings from Bemis and Seegal (1999). HCB was found to have greater than additive effects on TCDD’s reduction of body and thymus weight. This is important in addressing the importance of monitoring dietary sources, specifically fish consumption by pregnant women. It is apparent that the toxicant effects of methylmercury levels in fish are not acting in a singular nature. The health impacts these contaminant levels may have may be greater than what would be expected from high methylmercury levels alone. The capacity to evaluate the interaction profile of a mixture containing all five chemicals is not available. However, the joint toxic action of these chemicals on various endpoints is likely (Pohl et al., 2003).

### Table 6. ATSDR Chemical Mixtures & Health Effects

<table>
<thead>
<tr>
<th>Chemical Mixture</th>
<th>Primary Pathway</th>
<th>Primary Health Effects</th>
<th>Synergistic Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lead, Arsenic, Cadmium &amp; Chromium</td>
<td>Oral (contaminated soil/groundwater)</td>
<td>Neurological Carcinogenic Cardiovascular Reproductive</td>
<td>Additive, particularly for neurological impacts.</td>
</tr>
<tr>
<td>Benzene, Toluene, Ethylbenzene, and Xylenes (BTEX)</td>
<td>Air (volatilization and inhalation), water (drinking), &amp; contaminated soil. Each chemical is volatile and easily metabolized.</td>
<td>Neurological Carcinogenic Reproductive Immunologic Developmental Endocrine</td>
<td>Additive</td>
</tr>
<tr>
<td>Lead, Manganese, Zinc &amp; Copper</td>
<td>Oral (contaminated soil)</td>
<td>Neurological Carcinogenic Cardiovascular Reproductive</td>
<td>Manganese increases neurological toxicity of lead, but otherwise interactive effects less than additive.</td>
</tr>
<tr>
<td>Persistent chemicals in breast milk (methyl-mercury, dioxins, DDE, hexachlorobenzene, PCBs)</td>
<td>Oral</td>
<td>Developmental Neurotoxic Carcinogenic Developmental Endocrine Reproductive</td>
<td>Additive. Neurological &amp; developmental effects to be assumed as measure of public health safety.</td>
</tr>
<tr>
<td>Persistent chemicals in fish (methyl-mercury, dioxins, DDE, hexachlorobenzene, PCBs)</td>
<td>Oral</td>
<td>Developmental Neurotoxic Carcinogenic Developmental Endocrine Reproductive</td>
<td>Additive. Neurological &amp; carcinogenic effects to be assumed as measure of public health safety.</td>
</tr>
<tr>
<td>Compound Set</td>
<td>Exposure Route</td>
<td>Carcinogenic</td>
<td>Neurotoxic</td>
</tr>
<tr>
<td>--------------</td>
<td>----------------</td>
<td>--------------</td>
<td>------------</td>
</tr>
<tr>
<td>Cesium, Cobalt, PCBs, Strontium, &amp; Trichloroethylene</td>
<td>Oral (contaminated soil/groundwater)</td>
<td>Carcinogenic</td>
<td>Neurotoxic</td>
</tr>
<tr>
<td>Arsenic, Hydrazines, Jet Fuels, Strontium-90, &amp; Trichloroethylene</td>
<td>Oral (contaminated soil/groundwater) &amp; inhalation of volatile substances</td>
<td>Immunologic</td>
<td>Carcinogenic</td>
</tr>
<tr>
<td>Atrazine, Deethylatrazine, Diazinon, Nitrate, &amp; Simazine</td>
<td>Oral (contaminated groundwater &amp; well water)</td>
<td>Neurotoxic</td>
<td>Hematological</td>
</tr>
<tr>
<td>Chlorpyrifos, Lead, Mercury, and Methylmercury</td>
<td>Oral (ingestion in food)</td>
<td>Cardiovascular</td>
<td>Immunotoxic</td>
</tr>
</tbody>
</table>

Other studies of synergistic effects have taken place. For example, mercury chloride (HgCl₂) and 4-nonylphenol (NP) are widespread environmental and industrial pollutants that are known to have toxic effects as well as endocrine disrupting activities. Although the individual effects of HgCl₂ and NP in liver have been relatively well recognized, little is known about the interaction of NP and HgCl₂ during the induction of their toxicity. Lee et al. (2009) investigated the synergism between HgCl₂ and NP. They found that HgCl₂ and NP induced a significant cytotoxicity at concentrations where neither of them have any cytotoxic effect alone. The cytotoxicity of NP is enhanced in the presence of HgCl₂ and vice versa. Lee et al. (2009) conclude that their study suggests a mechanism of potential synergistic adverse effects of these toxic pollutants.
Polycyclic aromatic hydrocarbons (PAHs) and arsenic are both environmental agents that are known to have significant immunotoxicity. Previous studies have shown that PAH exposure of spleen cells in vitro produces significant immune suppression of humoral innate immunity. A study by Qian et al. (2010) examined the immunotoxicity of PAHs and arsenite following co-exposures with the theory being that the agents may exert synergistic actions, which might be based on their different mechanisms of action. PAH metabolites were found to be more potent than parent compounds in producing immunosuppression. Interestingly, a potent carcinogenic PAH not previously characterized for immunotoxicity, was also found to be strongly immunosuppressive. Co-exposure of spleen cell cultures to PAHs and arsenite, both at individual low-effect concentrations, was found to produce profound suppression demonstrating synergy between these two chemical classes of agents.

Historical exposures may interact with present day ones. Environmental exposure to persistent organic pollutants (POPs) may cause detrimental health effects in the population with the developing fetus and infants being at highest risk. Röllin et al. (2009) report on the findings of a pilot study that took place in seven geographical regions of South Africa, with 96 pregnant women admitted for delivery participated in the study. The overall results showed large regional differences, with the rural site having the lowest levels for all measured contaminants. The levels of PCB congeners were found to be low in all samples and across all sites. DDT metabolites were detected in most participants of this study and large regional differences were evident. Two malaria endemic sites, where indoor residual spraying with DDT takes place to control the malaria vector, were included in the study. The highest levels of DDT were measured in the coastal malaria site (Indian Ocean) with the inland malaria site to have elevated results as well. Röllin et al. (2009) conclude that the high DDT levels in the malaria spraying regions are concerning and call for extended monitoring of women and children in selected regions.

**Low Birth Weight**

Even though evidence linking ambient air pollution with mortality and respiratory morbidity in human beings has accumulated over the past 30 years, researchers have only recently begun to explore its influence on less traditional end-points and organs such as the cardiovascular system and heart and adverse pregnancy outcomes. Pregnancy may constitute a period of human development particularly susceptible to toxins contained in air pollution because of high cell proliferation, organ development and the changing capabilities of fetal metabolism. Importantly, the fetal origins hypothesis suggests that growth and developmental delays in utero may influence not only childhood mortality and morbidity but also the risk for diseases of the heart and metabolism, including diabetes in adulthood (Ritz and Wilhelm, 2008).

The well-accepted link between maternal smoking and adverse birth outcomes lends support for a role of ambient (outdoor) air pollution impacts on pregnancy. In the past decade, linkage of registry data such as birth certificates, with exposure measures based on routine monitoring data has resulted in a fast-growing body of evidence of air pollution’s harmful impact on fetal development. These studies have linked a number of air pollutants to outcomes, including low birthweight (LBW) and small for gestational age (SGA), prematurity, and cardiac birth defects. More recently, researchers also started to investigate pre-eclampsia and spontaneous abortion. All of the routinely measured ‘criteria’ air pollutants (i.e., carbon monoxide, PM$_{10}$, PM$_{2.5}$, nitrogen dioxide, ozone, sulfur dioxide) and, in
addition, polycyclic aromatic hydrocarbons (PAHs), have been linked to various measures of SGA mostly in urban areas throughout the world (Ritz and Wilhelm, 2008). Ritz and Wilhelm’s (2008) studies conducted in the South Coast Air Basin of California, found positive associations between last trimester exposures to carbon monoxide and PM$_{10}$ and term LBW. Associations between air pollution and preterm and low weight birth have also been documented not only in more polluted regions like the Los Angeles basin, but also in other urban areas with lower air pollution levels (Ritz and Wilhelm, 2008).

Furthermore, certain subpopulations of women and fetuses may be especially susceptible to air pollutants, such as individuals with a compromised general health status or those with social disadvantage that translate into increased exposure to toxins environmentally or occupationally, adverse behaviours (i.e., poorer diet, alcohol use and smoking) and lack of adequate access to health care and preventative health measures (Ritz and Wilhelm, 2008). In the above mentioned Los Angeles study, it was observed that traffic-related air pollution exposure disproportionately affected low income and disadvantaged neighbourhoods in the winter, when pollutant levels tend to peak due to meteorological conditions. These associations resulted in the highest odds of preterm birth for African Americans, Hispanics, and mothers <20 years and 35 years or older. Further work in this regard has been hampered by difficulties in rectifying differences between studies in definition of outcomes, number and type of pollutants and covariates considered, pregnancy exposure periods evaluated, and due to inconsistencies in reporting (e.g., scaling of pollutants or use of quartiles to define exposure categories) (Ritz and Wilhelm, 2008).

Brauer et al. (2008) evaluated the impacts of air pollution on small for gestational age (SGA) birth weight, low full-term birth weight (LBW), and preterm birth using spatiotemporal exposure metrics. With linked administrative data, they identified 70,249 singleton births (1999–2002) with complete covariate data (sex, ethnicity, parity, birth month and year, income, education) and maternal residential history in Vancouver, British Columbia. Brauer et al. (2008) estimated residential exposures by month of pregnancy chemicals and proximity to major roads. Residence within 50 meters of highways was associated with a 26% increase in SGA and an 11% increase in LBW. Exposure to all air pollutants except ozone was associated with SGA. For preterm births, associations were observed with PM$_{2.5}$ for births < 37 weeks gestation (and for other pollutants at < 30 weeks). No consistent patterns suggested exposure windows of greater relevance. Associations between traffic-related air pollution and birth outcomes were observed in a population-based cohort with relatively low ambient air pollution exposure.

**Other Reproductive Outcomes**

Several studies have detected relationships between particulate air pollution and lung cancer leading investigators to consider the genotoxicity of air pollution. Effects concerning reproduction are of special interest. In one of the few prospective studies, PAHs were measured by hair monitoring in the homes of NYC mothers during the last trimester of pregnancy. PAH air measurements were compared to rates of chromosomal aberrations through cord blood sampling. There was a significant positive relationship between the PAH exposure level and the number of stable mutations observed in cord blood. As it is not possible that mothers’ cord blood characteristics influenced air quality, this statistical association strongly suggests that air quality influenced the mutation rate. However, these
mutations occurred in somatic cells, not germ cells, and consequently have less evolutionary significance. However, heritable mutations may be increased by exposure to air pollution, specifically to particulates (Schell et al., 2010).

Other types of exposure also have been linked to influences on reproduction and the development of the reproductive system. Numerous studies of laboratory animals report effects of many pollutants on sperm and testicular development and these suggest that effects in humans are plausible. There also is a voluminous literature on variation in measures of sperm quality in humans. Using ecological designs, some authors have described temporal changes, usually declines, in measures of sperm quality within a specific population, and some suggest a possible association between those declines and changes in exposure to xenobiotics in the same population (Schell et al., 2010).

Recently studies of phthalates have also been shown to affect male morphology. Ano-genital distance is a morphological dimension that is sexually dimorphic being greater in males of many mammalian species including humans. A study of three to twenty-four-month-old boys found reduced ano-genital distance corrected for body weight in relation to measured levels of phthalate metabolites in maternal urine collected in the prenatal period. Phthalate levels were also associated with altered steroid hormone homeostasis in a Danish-Finnish cohort of three-month-old males (Schell et al., 2010).

Lead is a common pollutant of industrialized environments and in the current range of exposures is well known for its negative effects of neurological development and neurological functioning. Even though lead at high doses is a well known abortifacient, its endocrine disrupting properties had not been thoroughly investigated. Now substantial evidence has accumulated for its role as an endocrine disruptor. Maturational delay, in the form of greater age at menarche, is associated with lead levels in the U.S. population according to two analyses of NHANES data; the conclusions of these studies apply to most populations with mundane, chronic exposures, and not merely to the most highly exposed individuals (Schell et al., 2010).

Other persistent organic pollutants have also been investigated. Polybrominated biphenyls have been associated with an earlier age at menarche among girls in Michigan, USA; and polychlorinated aromatic hydrocarbons (PAHs) were associated with delayed sexual maturation. Several studies have not observed associations between pollutants and sexual maturation. Variation in results suggests that some influences are not controlled; differences in exposure levels and the timing of exposures may play roles in producing the differences in effects (Schell et al., 2010).

**Developmental and Neurological Impacts**

Empirical support for environmental toxins as a broad class has been quietly accumulating in research on autism spectrum disorder. Recent research has shown that persons with autism spectrum disorder have comparatively higher levels of various toxins and are more likely to have reduced detoxifying ability, and, that rates of autism spectrum disorder may be higher in areas with greater pollution. These results fit well with very recent research that shows that autism spectrum disorder rates are higher in California where pesticide use is very high, and with research that shows in Texas, rates are higher near toxic releasing industries (DeSoto, 2009).
Temporal exposure patterns during pregnancy may be relevant in relation to susceptibility “windows” of the fetal brain to methylmercury. Because developmental stages occur in temporally distinct time frames across the various brain regions, methylmercury may induce different regional effects depending on the timing of exposure. Methylmercury adverse effects on the developing brain have been proposed to be more a function of episodic high-level peak exposures than of average continuous exposures over the course of pregnancy, even though the average body burdens may be similar (Castoldi et al., 2008).

In 1987, a cohort study was initiated in the Amsterdam/Zaandam region of The Netherlands to study possible effects of dioxins on development and growth in a population of breastfed children selected after an optimal pregnancy and delivery and birth weight above 2500 grams. Effects on thyroid hormone metabolism, liver, haematology and immunology, and retinol binding protein were found in neonates. Follow-up was performed at the age of 2½ years, 8-12 years and 13-18 years. Negative effects on lung function and on brain development (studied with neurophysiological tests of visuo-motoric and cognitive performance) were demonstrated in the age of 8-12 years. In adolescence preliminary results show a delay of almost 1 year in breast development in girls in association with higher prenatal dioxin exposure and again a negative effect on innate immunity (Leijs et al., 2008).

**Diabetes, Overweight and Obesity**

Air pollution is associated with an increased risk for cardiovascular events; however, many of the biological pathways involved could also promote diabetes mellitus. A study between two respiratory clinics in Toronto and Hamilton, Ontario showed there were no positive associations between air pollution and diabetes among men. Exposure to nitrogen dioxide, a marker of traffic-related air pollutants, was associated with diabetes prevalence among women. The results suggest that common air pollutants are associated with diabetes and warrant more investigation to determine if this is a cause-and-effect relationship (Brook et al., 2008).

In another study, a heavily polluted area of Eastern Slovakia was targeted to search for possible links between environmental pollution and both pre-diabetes and diabetes. Associations of serum levels of five persistent organic pollutants: PCBs, DDE, DDT, HCB and β-hexachlorocyclohexane (β-HCH), with pre-diabetes and diabetes were investigated in 2,047 adults. It was found that increasing serum concentrations of individual persistent organic pollutants considerably increased prevalence of pre-diabetes and diabetes in a dose-dependent manner (Ukropec et al., 2010).

In Belgium, a study of 257 Belgian women and men compared levels of toxicants in diabetics and non-diabetics. The participants lived near steel plants, waste incinerators, and industrial areas where substantial exposure was expected, and from rural areas where much lower exposure was expected. Toxicants measured included PCDDs, PCDFs, coplanar PCBs (ones that resemble dioxin), and a group of 12 PCBs (considered a proxy of total PCB level). Diabetics had significantly higher levels of PCDDs, PCDFs, coplanar PCBs, and of 12 marker PCBs. Most toxicant levels were about twice as high in the diabetics than the non-diabetics and all were significantly different. The risk ratio for dioxin was 5.1, coplanar PCBs was 12.2, and 12 PCBs was 7.6 (Fierens et al., 2003).
A common source of persistent organic pollutants (POPs) is dietary fish. POPs are lipophilic and piscivorous fish bioconcentrate POPs. Large, older piscivorous fish that are higher up the food chain have higher concentrations. A study of Swedish fishermen and their partners in whom exposure is largely from the consumption of fatty fish from the Baltic demonstrate clear differences in the body burden of toxicant levels between diabetics and non-diabetics. Classification was based on self reported and was supported by evaluation of medications. When grouped by terciles of exposure, the ratio for persons with diabetes to those without increased with increasing exposure. Differences in toxicant burdens between diabetics and non-diabetics were statistically significant (Schell et al., 2010).

These studies are not isolated findings. One study found elevated odds ratios of diabetes associated with several POPs including PCBs, DDT (measured as its metabolite, DDE) and most clearly with hexachlorobenzene. Analysis of NHANES data (1999–2002) found strong associations between six POPs including certain PCBs and dioxins with well defined diabetes status after adjustment for age, sex, race/ethnicity, poverty income ratio, body-mass index and waste circumference. Follow-up studies with the same dataset indicated especially strong associations with PCBs and organochlorine pesticides. Clearly, further investigation is warranted as the interrelationship of dietary fat, POP intake, overweight/obesity and diabetes is complex. Although the emphasis here has been on POPs and diabetes, very recent in vivo experiments have shown that mercury can induce oxidative stress causing pancreatic beta-cell dysfunction and cytotoxicity (Schell et al., 2010).

Overweight and obesity are often associated with diabetes. Overweight and obesity are well-known risk factors for type II diabetes as well as other diseases including the cardiovascular diseases. Although most have regarded nutritional factors during prenatal or postnatal life as only risk factors for overweight and obesity, other factors are now considered seriously including sleep and pollutant burden. Several POPs are associated with overweight and obesity. For example, the risk of overweight and obesity was 2.5 and 3.0 times greater, respectively, among Spanish 6.5-year-olds whose cord blood level of hexachlorobenzene was above 1.6 ng/mL versus children whose level was 0.46 ng/mL or less. Among children in the normal ranges of weight, a positive correlation was found also. These children had only mundane exposure to this pollutant and a body burden common to many children today. Other studies have found similarly elevated risk of overweight and or obesity in connection with exposure to these and other POPs. A possible mechanism is through thyroid regulated pathways. Thyroid hormones are associated with weight change, and several studies have observed alterations in thyroid hormone levels in conjunction with exposure to POPs (Schell et al., 2010).

**EMERGING PATHWAYS OF CONCERN**

The main pathways of concern for the potential transfer of contaminants in the Great Lakes remain air and water. Others are emerging and we highlight some of these in the following sections.

**Prenatal Exposure**

Inner-city minority populations are high-risk groups for adverse birth outcomes and also more likely to be exposed to environmental contaminants, including environmental tobacco smoke (ETS),
benzo(a)pyrene (B(a)P), other ambient polycyclic aromatic hydrocarbons (PAHs), and residential pesticides. The Columbia Center for Children’s Environmental Health (CCCEH) conducted a study of 700 northern Manhattan pregnant women and newborns to examine the effects of prenatal exposure to these common toxicants on fetal growth, early neurodevelopment, and respiratory health. Perera et al. (2005) summarize results of three published studies from this cohort demonstrating the effects of prenatal ETS, PAH, and pesticides on birth outcomes and/or neurocognitive development. Self-reported ETS was associated with decreased head circumference, and there was a significant interaction between ETS and B(a)P-DNA adducts such that combined exposure had a significant multiplicative effect on birth weight and head circumference after adjusting for confounders. A second analysis examined the neurotoxic effects of prenatal ETS exposure and postpartum material hardship (i.e., unmet basic needs in the areas of food, housing, and clothing) on 2-year cognitive development. Both exposures depressed cognitive development, and there was a significant interaction such that children with exposure to both ETS and material hardship exhibited the greatest cognitive deficit. A third analysis found that cord chlorpyrifos, and a combined measure of cord chlorpyrifos, diazinon, and propoxur-metabolite, were inversely associated with birth weight and/or length.

Chen et al. (2002) compared the cognitive development in Taiwanese children who had been exposed prenatally to high levels of heat-degraded PCBs with control children who were exposed to background levels. The disorder was called Yu-Cheng, "oil disease," in a Taiwanese matched-pair cohort study. The study population was one hundred eighteen children born between June 1978 and March 1985 during or after their mothers' consumption of contaminated rice oil; 118 children matched for age, sex, neighborhood, maternal age, and parental education and occupational class; and 15 older siblings of exposed children, born before the poisoning. The exposed children scored approximately 5 points lower on the Stanford-Binet test at the ages of 4 and 5 years and approximately 5 points lower on the Wechsler Intelligence Scale for Children, Revised, at the ages of 6 and 7 years. Children born up to 6 years after their mothers' exposure were as affected as children born within a year or two after exposure when examined at 6 and 7 years of age. Older siblings resembled the control children. Thus children prenatally exposed to heat-degraded PCBs had poorer cognitive development than their matched controls. The effect persisted in the children up to the age of 7 years, and children born long after the exposure were still affected.

Another area of concern with respect to prenatal exposure is the time lag between methylmercury exposure and onset of the effect that can complicate the interpretation of epidemiological data. In some cases the effects of prenatal methylmercury exposure did not become evident until adult life. Delayed methylmercury neurotoxicity has been reproduced in animal models. In monkeys receiving a low daily dose of methylmercury for the first 7 years of life, no signs of poisoning developed until 13 years of age, that is after a latent period of 6 years. A study of Cree Indian children aged 12–30 months demonstrated abnormality of the tendon reflexes which was positively associated with methylmercury exposure only in boys. According to a retrospective study of Minamata disease, there was a reduced male birth ratio associated with increased male fetal death at the time of the methylmercury epidemics in the 1950s in Japan. Gender-specific effects of methylmercury have been reproduced experimentally. In rats perinatally exposed to methylmercury behavioural alterations suggestive of altered dopaminergic neurotransmission were observed in males only, both at weaning and adult age. Gender-related differences in methylmercury metabolism and in antioxidant defences have been proposed to contribute to the differential susceptibility of males and females to this compound (Castoldi et al., 2008).
**Exposure Through Breast Milk**

Breastfeeding has been recognized and promoted by public health officials as the most beneficial source of nourishment during infancy. However, potential risks associated with breastfeeding also need to be factored into the overall public health assessment when women are encouraged to breastfeed their newborn infants. Breastfeeding for nursing infants can be a potential source of exposure to toxic chemicals to which the mother has previously been exposed. This may be true for two major reasons. First; breastfeeding serves as a food source for this segment of the human population: the diets of many newborns are limited to breast milk or it is at least a major nutrient source for suckling infants. Second; breastfed infants are at the top of the food chain. Therefore, chemicals accumulated in the mother’s tissues, may be transferred to infant during breastfeeding. This is especially true for environmental lipid-soluble pollutants such as polyhalogenated chemicals, because these chemicals tend to slowly degrade in the environment, to bioaccumulate and to bioconcentrate in the food chain, having long half-lives in humans. Because of the milk fat content is relatively high, breastfeeding potentially causes high-dose exposure of lipid-soluble pollutants (Massart et al., 2008).

In a review, Massart et al. (2008) comment on many pollutants, including dioxins and furans. Dioxins and furans are two closely related groups of chemical by-products that are produced throughout the world. Dioxins and furans are listed by several governmental and international agencies as known causes of human cancers hormone/reproductive disruptions, fetal abnormalities and immune alterations. Because dioxins and furans are environmentally persistent, lactation is one of the main routes of excretion. The dioxin and furan congeners thought to be most toxic to humans are 7 dioxins and 10 furans known as the 2, 3, 7, 8-congeners. In breast milk monitoring studies, the term “dioxin” refers to this group of 17 congeners. Unlike other contaminants, there has been considerable work showing the effects of dioxin exposure at low levels near the range detected in breast milk.

Dioxins and furans have been breast milk-measured in at least 35 countries. It has been well established in the literature that dioxin exposures were higher during the middle decades of the 20th century than they are now and that body burdens in older individuals are currently significantly higher than in younger individuals. However, the general time trend in many countries seems to be toward a slight decrease of dioxin levels in breast milk over past decade. In some countries, the decrease has been quite dramatic, with levels reduced by as much as 50%. Coordinated WHO studies in Europe from 1986 to 1993 showed an average decrease in dioxin levels of approximately 35%, with consistently higher levels in industrial areas (Massart et al., 2008).

Massart et al. (2008) also examined heavy metals, such as lead, mercury and cadmium which have been reported in breast milk monitoring studies. Their mean values in human milk vary in a wide range. Indeed, mean lead concentrations ranged from 5 to 277 mg/ml until 1973 and recently reported a breast milk lead content of 3.1–117.4 μg/l in Moroccan women. In a Turkish study, breast milk values of lead and cadmium were 14.6 μg/l and 2.8 μg/l, respectively. On the other hand, cadmium (0.14–0.19 μg/l) and lead (0.15–0.48 μg/l) ranges recently reported in Greek population were among the lowest reported in the literature. Worldwide mercury contaminations ranging from 0.03 ng/ml in Canada to 200 ng/ml in Iraq have also been reported.
This wide variation shows a strong dependence of heavy metal content on various factors including the local environment, socioeconomic conditions of the family and local diet and habits. For example, plant workers showed the higher presence of heavy metals (e.g., lead, mercury and manganese) in their breast milk and blood samples compared to the residents of the area and the subjects living outside the industrial environment, respectively. A recent study showed that the mother’s place of residence plays a significant role in breast milk lead content: mothers living in urban areas had higher lead concentration in breast milk compared to those living in rural areas. This difference is most likely due to the higher traffic density within the cities. The majority of previous studies supported the view that women living in the urban areas with heavy road traffic and industrial activity have breast milk lead concentrations significantly higher than women leaving in rural areas (Massart et al., 2008).

In mature milk, positive associations between breast milk mercury and fish consumption and between breast milk mercury and amalgam fillings have been demonstrated. However, in transitional milk, such associations were not statistically significant. On the other hand, cadmium levels in breast milk are significantly associated with cigarette smoking. One German study showed a direct relationship between the number of cigarettes a mother smokes per day and breast milk cadmium level. It is interesting to note that some studies indicate that infant’s exposure to cadmium from soy formula is about 20-fold higher than breast milk levels (Massart et al., 2008).

Unlike other persistent organic pollutants, heavy metals (i.e., lead, mercury and cadmium) appear in human milk at smaller concentrations than lipid-soluble chemicals and are about 20% of the level found in blood from the same person. This is attributed to their low lipid-solubility and high binding to erythrocytes. As a result, infants are likely to be exposed to higher levels before birth than during breastfeeding. Nonetheless, toxic metals in breast milk are important as additional pathway of exposure and as indicator of likely prenatal exposures (Massart et al., 2008).

**Gene-Environment Interactions**

Hunter (2005) suggests the following reasons for examining gene-environment interactions:

- Obtain a better estimate of the population-attributable risk for genetic and environmental risk factors by accounting for their joint interactions.
- Strengthen the associations between environmental factors and diseases by examining these factors in genetically susceptible individuals.
- Help to dissect disease mechanisms in humans by using information on susceptibility (and resistance) genes to focus on the biological pathways that are most relevant to that disease, and the environmental factors that are most relevant to the pathways.
- Determine which specific compounds in the complex mixtures of compounds that humans are exposed to (such as diet or air pollution) cause disease.
- Use the information on biological pathways to design new preventive and therapeutic strategies.
- Offer tailored preventive advice that is based on the knowledge that an individual carries susceptibility or resistance alleles.

Wang et al. (2007) examine particulate air pollution and cardiovascular mortality and morbidity; transition metals such as iron bound to the particles may be responsible for those associations. The
protein product of the hemochromatosis gene modulates uptake of iron and divalent cations from pulmonary sources and reduces their toxicity. Two hemochromatosis polymorphisms associated with increased iron uptake may modify the effect of metal-rich particles on the cardiovascular system. Wang et al. investigated the association between particulate matter $\leq 2.5 \mu m$ in aerodynamic diameter and heart rate variability in 518 older men from the Normative Aging Study who were examined between November 2000 and December 2004. A 10-microg/m$^3$ increase in particulate matter $\leq 2.5 \mu m$ in aerodynamic diameter during the 48 hours before heart rate variability measurement was associated with a 31.7% decrease in the high-frequency component of heart rate variability in persons with the wild-type genotype, whereas no relationship in the high-frequency component was observed in persons with either hemochromatosis variant. The difference in effect of PM$_{2.5}$ on the high-frequency component between persons with and without hemochromatosis variants was significant. Thus the effect of particles on cardiac autonomic function was shielded in subjects with at least 1 copy of a hemochromatosis variant compared with wild-type subjects. Transition metals, including iron, bound to ambient particles and the related oxidative stress may play an important role in cardiac toxicity of particles.

Peters et al. (2009) offer that there is evidence suggesting that cardiovascular effects of air pollution are mediated by systemic inflammation which is regulated by genes involved in these pathways. City-specific analyses were conducted using additive mixed models adjusting for patient characteristics, time trend and meteorology to assess the impact of air pollutants on plasma fibrinogen levels modified by the selected single nucleotide polymorphisms. They identified 39 single nucleotide polymorphisms in 14 gene loci associated with increased variability of fibrinogen levels. Testing for gene-environment interactions, for subjects being homozygous for the minor allele of TLR4 rs2770150 a 2.4% percent increase in fibrinogen mean per 13.5 $\mu g/m^3$ increase in the 5-day-average of particles with a diameter $< 10 \mu m$ was found, whereas for subjects being homozygous for the major allele no change in fibrinogen was seen. Peters et al. (2009), therefore, identified new potential pathways of genetic modulation of the air pollution-fibrinogen response in myocardial infarction survivors.

High total plasma homocysteine (tHcy) is a risk factor for human health. Ambient particulate matter is also associated with cardiovascular events and, recently, with tHcy. However, the biological mechanisms are not fully understood. One of the putative pathways is through oxidative stress. Ren et al. (2009) used repeated measures data from the Normative Aging Study to examine whether the associations of PM$_{2.5}$ and black carbon with tHcy were modified by a broad set of genetic polymorphisms related to oxidative stress. PM$_{2.5}$, black carbon, tHcy and other covariates were repeatedly measured between 1995 and 2006. Several gene polymorphisms marginally modified effects of PM$_{2.5}$ and black carbon. All genes with significant interactions with particulate air pollution had marginally significant main effects on tHcy. Ren et al. conclude that the effects of PM$_{2.5}$ and black carbon on tHcy appeared to be mediated by genes related to oxidative stress pathways.

In their recent review, Ober and Vercelli (2011) examine environmental tobacco smoke (ETS) exposure in early life as a well-established risk factor for reduced lung function, increased numbers of lower respiratory tract infections and asthma. However, not all exposed children show these effects. Interactions between in utero or neonatal exposure to ETS and several genetic loci were first suggested by family-based linkage studies, with some chromosomal regions showing linkage to asthma or bronchial hyper-responsiveness only in exposed children or only in non-exposed children. The 5q region, which harbours many asthma candidate genes, was linked to asthma in the exposed
children in two studies; one other region showed interaction effects in two studies but in opposite groups (in exposed children in one study and in non-exposed children in the other). During the past 3 years alone, the effects of interactions between in utero or neonatal ETS exposure and genotypes at candidate loci on risk for asthma or wheezing have been reported. In all but one of these studies, associations with asthma were significant in exposed children only. In all three studies, the linkage and or association with asthma was only among children exposed to ETS in utero or in the first year of life, providing consistent evidence for an \( 'IL13\)–ETS exposure’ association with asthma risk. Accounting for this easily measurable exposure in genetic studies might enhance the ability of researchers to identify important risk loci.

Furthermore, maternal asthma remains among the most significant risk factors for the development of childhood asthma in offspring. Because asthma risk alleles are inherited from both parents, this suggests that the in utero environment differs between mothers with and without asthma. Such differences could result in differential ‘prenatal programming’ of immune cells in the fetus, depending on the asthma status of the mother, or from exposure to asthma medications (e.g. corticosteroids) taken by asthmatic mothers during pregnancy. Evidence that the fetal genotype interacts with ‘maternal asthma’ to determine risk for asthma in the child was first provided by a positional cloning study that identified human leukocyte antigen (\( HLA\))-\( G\) as an asthma susceptibility gene. In that study, the \(-964G\) allele was associated with asthma only in families with an affected mother, and the \(-964A\) allele was associated with asthma in families with an unaffected mother. Paternal asthma status had no effect. Moreover, the parental origin of the fetal alleles had no effect on risk, indicating that paternal imprinting is not involved. The mechanism through which the ‘maternal asthma–fetal HLA-G genotype’ interaction influences subsequent risk for asthma in the child is still unknown, but modulation of expression via miRNA targeting could be involved. Because asthma in the mother is such a strong predictor of asthma in her children, it is probable that other, as yet undiscovered, genes also have a role in modulating this effect (Ober and Vercelli, 2011).

Much of this research is new and appears in conference abstracts. And as Ober and Vercelli (2011) conclude by agreeing that animal models are often proposed as powerful tools for studies of complex interactions and can provide valuable insights into the architecture of gene–gene, gene–environment and gene–gene–environment interactions. It is, however, unclear that animal models will offer insights into specific interactions contributing to disease risk in humans because of the context dependency of these effects. By contrast, cellular human models might provide one approach and a reasonable compromise for studies of gene-environment interactions. Although these studies will sacrifice organismal context, cellular systems can reveal a finite number of genotype-dependent interactions occurring in response to specific ‘exposures’ under relatively controlled conditions and, in addition, allow direct studies of mechanism. Ober and Vercelli further suggest that this approach, applied to additional cell types and exposures, is a powerful tool both for identifying candidates that can be subjected to more targeted gene–environment interaction studies in human populations and for elucidating the mechanism(s) that underlie gene–environment interactions.

A complementary, and equally important, avenue of investigation is to characterize gene–environment interactions in human populations. The important question of how to maximize the ability to detect gene–environment interactions given their subtle effects and, therefore, elusive nature remains. A crucial consideration in this context is that most of the well-validated gene–environment interactions have not been found by chance. Rather, they were discovered using models
based on knowledge of biological processes and/or pathways. Gene–environment interactions are most likely to occur in, and impact on, signaling pathways regulated by threshold effects; that is, whenever quantitative differences in the intensity of the signal delivered by exogenous or endogenous stimuli result in qualitative differences in the outcome of that signal. In the immune system, for instance, weak versus strong signals can result in distinct and often opposite effects, particularly on cell fate determination. Such environmental stimuli and gain- or loss-of function variants in the receptors and/or adaptors that transduce these signals are excellent candidates for gene–environment interactions. Indeed, the reason why candidate gene studies have been so successful in discovering and characterizing gene–environment interactions might be that these studies have explicitly, or more often implicitly, focused on processes, such as innate immunity, in which the strength of the environmental signal has a pivotal role (Ober and Vercelli, 2011).

In conclusion, the evidence for gene–environment interactions in the literature is compelling, as is the argument that the failure to model gene–environment interactions in genetic studies will result in missing potentially important loci that show interactions, particularly those with ‘flip-flop’ patterns of association. Thus, although the ‘environment’ can be considered a ‘nuisance’ to genetic studies, Ober and Vercelli (2011) prefer to think of it as an outstanding ‘opportunity’ to understand disease heterogeneity, to provide clues to the causative pathways in asthma pathogenesis, and to inform on the complex genetic architecture of common diseases and quantitative phenotypes. Environment is currently defined broadly, i.e., virtually non-genetic influence but its potential role in physical and chemical environments cannot be overlooked. Thomas (2010) points to the promise of gene-environment association studies while discussing the methodological challenges. Furthermore, Rappaport and Smith (2010) point to the problems on relying on genetic investigation to understand genomes and questionnaires to examine environmental exposures. They write of the need to discover exposomes which would comprise a profile of the most prominent classes of toxicants that are known to cause disease, namely, reactive electrophiles, endocrine (hormone) disruptors, modulators of immune responses, agents that bind to cellular receptors, and metals. Exposures to these agents can be monitored in the blood either by direct measurement or by looking for their effects on physiological processes (such as metabolism). These processes generate products that serve as signatures and biomarkers in the blood.
Figure 8. Characterizing the Exposome

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Acknowledgements

This report updates but does not replace those of 2005 and 2007. As with those, this update is a broad-ranging review of many academic and policy literatures, some of which are cited in a near verbatim style. We gratefully acknowledge the roles of all the scientists whose work has made this update possible.
<table>
<thead>
<tr>
<th>Acronyms</th>
<th>Description</th>
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<tbody>
<tr>
<td>AhR</td>
<td>Aryl hydrocarbon Receptor</td>
</tr>
<tr>
<td>AOC</td>
<td>Areas of Concern</td>
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<tr>
<td>AR</td>
<td>Androgen Receptor</td>
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<tr>
<td>ATSDR</td>
<td>Agency for Toxic Substances and Disease Registry</td>
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<tr>
<td>BBP</td>
<td>Butyl Benzyl Phthalate</td>
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<tr>
<td>BPA</td>
<td>Bisphenol A</td>
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<tr>
<td>BPDE</td>
<td>BaP-7,8-diol-9,10-epoxide</td>
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<tr>
<td>BTEX</td>
<td>Benzene, Toluene, Ethylbenzene, and Xylenes compounds</td>
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<tr>
<td>CDC</td>
<td>Centers for Disease Control and Prevention</td>
</tr>
<tr>
<td>CEC</td>
<td>Commission for Environmental Cooperation</td>
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<tr>
<td>CEPA</td>
<td>Canadian Environmental Protection Act</td>
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<tr>
<td>CFC</td>
<td>Chlorofluorocarbons</td>
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<tr>
<td>COC</td>
<td>Chemicals of Concern</td>
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<td>CP</td>
<td>Chlorinated Paraffins</td>
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<tr>
<td>CPSC</td>
<td>U.S. Consumer Product Safety Commission</td>
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<tr>
<td>DBP</td>
<td>Disinfectant By-Products</td>
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<tr>
<td>DDT</td>
<td>Dichlorodiphenyltrichloroethane</td>
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<tr>
<td>DEHP</td>
<td>Di(2-ethylhexyl) Phthalate</td>
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<tr>
<td>DEP</td>
<td>Diethylphthalate</td>
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<tr>
<td>DIBP</td>
<td>Diisobutyl Phthalate</td>
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<td>DIDP</td>
<td>Diisodecyl Phthalate</td>
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<tr>
<td>DINP</td>
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<td>DMBA</td>
<td>7,12-dimethylbenz[a]anthracene</td>
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<tr>
<td>DPHP</td>
<td>Di-2-propylheptyl Phthalate</td>
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<td>DWT</td>
<td>Drinking Water Treatment Facility</td>
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<td>EDC</td>
<td>Endocrine Disrupting Chemicals</td>
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<td>EFSA</td>
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<td>EMEA</td>
<td>European Medicines Evaluation Agency</td>
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<td>EPA</td>
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<td>ER</td>
<td>Estrogen Receptor</td>
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<td>ERA</td>
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<td>ETS</td>
<td>Environmental Tobacco Smoke</td>
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<td>GLSCF</td>
<td>Great Lakes Sport-Caught Fish</td>
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<td>HBCD</td>
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<td>HCB</td>
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<td>HCRA</td>
<td>Harvard Center for Risk Analysis</td>
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<td>HLA</td>
<td>Human Leukocyte Antigen</td>
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<td>IJC</td>
<td>International Joint Commission</td>
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<tr>
<td>IQR</td>
<td>Interquartile Ranges</td>
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<td>LBW</td>
<td>Low Birthweight</td>
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<tr>
<td>LCCP</td>
<td>Long-Chained Chlorinated Paraffins</td>
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<tr>
<td>MBzP</td>
<td>Monobenzyl Phthalate</td>
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<tr>
<td>Abbreviation</td>
<td>Definition</td>
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<tr>
<td>MCCP</td>
<td>Medium-Chain Chlorinated Paraffins</td>
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<td>MCPP</td>
<td>Mono(3-carboxypropyl) Phthalate</td>
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<td>MCL</td>
<td>Maximum Contaminant Levels</td>
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<td>MEP</td>
<td>Monoethyl Phthalate</td>
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<td>MRL</td>
<td>Minimal Risk Level</td>
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<td>NHANES</td>
<td>National Health and Examination Survey</td>
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<td>NIH</td>
<td>United States’ National Institute of Health</td>
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<td>NP</td>
<td>Nonylphenol Ethoxylates</td>
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<td>NPE</td>
<td>Nonylphenol Ethoxylates</td>
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<td>NPDES</td>
<td>National Pollutant Discharge Elimination System</td>
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<td>NPRI</td>
<td>National Pollutant Release Inventory</td>
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<tr>
<td>NRC</td>
<td>National Research Council</td>
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<tr>
<td>NTP</td>
<td>National Toxicology Program</td>
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<tr>
<td>OC</td>
<td>Organochlorine Pesticide</td>
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<tr>
<td>OP</td>
<td>Organophosphate Pesticide</td>
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<td>PAH</td>
<td>Polycyclicaromatic Hydrocarbons</td>
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<td>PBB</td>
<td>Polybrominated Biphenyls</td>
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<td>PBDE</td>
<td>Polybrominated Diphenyl Ethers</td>
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<td>PCB</td>
<td>Polychlorinated Biphenyls</td>
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<td>PCDD</td>
<td>Polychlorinated Dibenzodioxins</td>
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<td>PCDF</td>
<td>Polychlorinated Dibenzofurans</td>
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<td>PD</td>
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<td>PFC</td>
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<td>PFCA</td>
<td>Plaque-Forming Cell Assay</td>
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<td>PFOS</td>
<td>Perfluorooctanesulfonate</td>
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<td>POP</td>
<td>Persistent Organic Pollutants</td>
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<td>PPCP</td>
<td>Pharmaceuticals and Personal Care Products</td>
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<td>PRG</td>
<td>Preliminary Remediation Goals</td>
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<td>PVC</td>
<td>Polyvinyl Chloride</td>
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<td>RSL</td>
<td>Residential Soil Limit</td>
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<td>SCCP</td>
<td>Short-Chain Chlorinated Paraffins</td>
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<td>SGA</td>
<td>Small-for-Gestational-Age</td>
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<td>SRBC</td>
<td>Sheep Red Blood Cells</td>
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<td>TCC</td>
<td>Triclocarban</td>
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<tr>
<td>TCDD</td>
<td>2,3,7,8 Tetrachlorodibenzo-p-dioxin</td>
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<td>TCS</td>
<td>Triclosan</td>
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<tr>
<td>TDI</td>
<td>Tolerable Daily Intake</td>
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<td>TDS</td>
<td>Testicular Dysgenesis Syndrome</td>
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<td>TEF</td>
<td>Toxic Equivalent Factors</td>
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<tr>
<td>tHcy</td>
<td>Total Plasma Homocysteine</td>
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<td>THM</td>
<td>Trihalomethanes</td>
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<td>TNF</td>
<td>Tumour Necrosis Factor</td>
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<tr>
<td>TTHM</td>
<td>Total Trihalomethanes</td>
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<td>TRI</td>
<td>United States’ Toxic Release Inventory</td>
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<td>TSCA</td>
<td>Toxic Substances Control Act</td>
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<tr>
<td>Acronym</td>
<td>Description</td>
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<tr>
<td>UTR</td>
<td>Untranslated Region</td>
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<tr>
<td>VOC</td>
<td>Volatile Organic Compounds</td>
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Appendix 1


The Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA) [42 U.S.C. 9604 et seq.], as amended by the Superfund Amendments and Reauthorization Act (SARA) [Pub. L. 99-499], requires that the Agency for Toxic Substances and Disease Registry (ATSDR) develop jointly with the U.S. Environmental Protection Agency (EPA), in order of priority, a list of hazardous substances most commonly found at facilities on the CERCLA National Priorities List (NPL) (42 U.S.C. 9604(i)(2)); prepare toxicological profiles for each substance included on the priority list of hazardous substances, and to ascertain significant human exposure levels (SHELS) for hazardous substances in the environment, and the associated acute, subacute, and chronic health effects (42 U.S.C. 9604(i)(3)); and assure the initiation of a research program to fill identified data needs associated with the substances (42 U.S.C. 9604(i)(5)).

The ATSDR Minimal Risk Levels (MRLs) were developed as an initial response to the mandate. Following discussions with scientists within the Department of Health and Human Services (HHS) and the EPA, ATSDR chose to adopt a practice similar to that of the EPA’s Reference Dose (RfD) and Reference Concentration (RFC) for deriving substance specific health guidance levels for nonneoplastic endpoints. An MRL is an estimate of the daily human exposure to a hazardous substance that is likely to be without appreciable risk of adverse noncancer health effects over a specified duration of exposure. These substance specific estimates, which are intended to serve as screening levels, are used by ATSDR health assessors and other responders to identify contaminants and potential health effects that may be of concern at hazardous waste sites. It is important to note that MRLs are not intended to define clean up or action levels for ATSDR or other Agencies.

The toxicological profiles include an examination, summary, and interpretation of available toxicological information and epidemiologic evaluations of a hazardous substance. During the development of toxicological profiles, MRLs are derived when ATSDR determines that reliable and sufficient data exist to identify the target organ(s) of effect or the most sensitive health effect(s) for a specific duration for a given route of exposure to the substance. MRLs are based on noncancer health effects only and are not based on a consideration of cancer effects. Inhalation MRLs are exposure concentrations expressed in units of parts per million (ppm) for gases and volatiles, or milligrams per cubic meter (mg/m³) for particles. Oral MRLs are expressed as daily human doses in units of milligrams per kilogram per day (mg/kg/day). Radiation MRLs are expressed as external exposures in units of millisieverts.

ATSDR uses the no observed adverse effect level/uncertainty factor (NOAEL/UF) approach to derive MRLs for hazardous substances. They are set below levels that, based on current information, might cause adverse health effects in the people most sensitive to such substance induced effects. MRLs are derived for acute (1-14 days), intermediate (>14-364 days), and chronic (365 days and longer) exposure durations, and for the oral and inhalation routes of exposure. Currently MRLs for the dermal route of exposure are not derived because ATSDR has not yet identified a method suitable for this route of exposure. MRLs are generally based on the most sensitive substance-induced end point considered to be of relevance to humans. ATSDR does not use serious health effects (such as
irreparable damage to the liver or kidneys, or birth defects) as a basis for establishing MRLs. Exposure to a level above the MRL does not mean that adverse health effects will occur.

MRLs are intended to serve as a screening tool to help public health professionals decide where to look more closely. They may also be viewed as a mechanism to identify those hazardous waste sites that are not expected to cause adverse health effects. Most MRLs contain some degree of uncertainty because of the lack of precise toxicological information on the people who might be most sensitive (e.g., infants, elderly, and nutritionally or immunologically compromised) to effects of hazardous substances. ATSDR uses a conservative (i.e., protective) approach to address these uncertainties consistent with the public health principle of prevention. Although human data are preferred, MRLs often must be based on animal studies because relevant human studies are lacking. In the absence of evidence to the contrary, ATSDR assumes that humans are more sensitive than animals to the effects of hazardous substances that certain persons may be particularly sensitive. Thus the resulting MRL may be as much as a hundredfold below levels shown to be nontoxic in laboratory animals. When adequate information is available, physiologically based pharmacokinetic (PBPK) modeling and benchmark dose (BMD) modeling have also been used as an adjunct to the NOAEL/UF approach in deriving MRLs.

Proposed MRLs undergo a rigorous review process. They are reviewed by the Health Effects/MRL Workgroup within the Division of Toxicology and Environmental Medicine; and expert panel of external peer reviewers; the agency wide MRL Workgroup, with participation from other federal agencies, including EPA; and are submitted for public comment through the toxicological profile public comment period. Each MRL is subject to change as new information becomes available concomitant with updating the toxicological profile of the substance. MRLs in the most recent toxicological profiles supersede previously published levels. To date, 143 inhalation MRLs, 241 oral MRLs and 8 external radiation MRLs have been derived. A listing of the current published MRLs by route and duration of exposure is provided as follows.

To view ATSDR’s Minimal Risk List, see: http://www.atsdr.cdc.gov/mrls/pdfs/atsdr_mrls_december_2010.pdf