THERE IS NO "AWAY"

PHARMACEUTICALS, PERSONAL CARE PRODUCTS, AND ENDOCRINE-DISRUPTING SUBSTANCES: EMERGING CONTAMINANTS DETECTED IN WATER

CANADIAN INSTITUTE FOR ENVIRONMENTAL LAW AND POLICY

L'INSTITUT CANADIEN DU DROIT ET DE LA POLITIQUE DE L'ENVIRONNEMENT

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There Is No "Away."
Pharmaceuticals, Personal Care Products, and Endocrine-Disrupting Substances: Emerging Contaminants Detected in Water

by Susan Holtz
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January 2006

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Founded in 1970, as the Canadian Environmental Law Research Foundation (CELRF), the Canadian Institute for Environmental Law and Policy (CIELAP) is an independent, not-for-profit professional research and educational institute committed to environmental law and policy analysis and reform. CIELAP is incorporated under the laws of the Province of Ontario and registered with Revenue Canada as a charitable organization. Our registration number is 11883 3417 RR0001.

CIELAP provides leadership in the research and development of environmental law and policy that promotes the public interest and sustainability.

About the Author

Susan Holtz is a policy consultant to CIELAP on issues related to sustainable development, water and energy. She also works on related issues as a mediator, facilitator, and editor. Mrs Holtz was the founding Vice Chair of both the Canadian and Nova Scotia Round Tables on the Environment and the Economy. Mrs Holtz was also instrumental in setting up the Canadian Environmental Network (CEN). She has served on many advisory bodies and boards, including the Auditor General of Canada's Panel of Senior Advisors and the Commissioner of Environment and Sustainable Development's External Advisory Panel.

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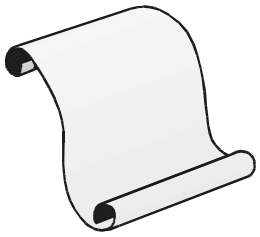
Summary

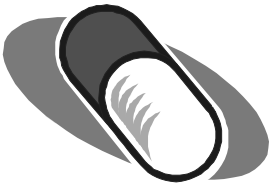
This report reviews the developing issue of emerging contaminants now being detected in water, including pharmaceuticals, personal care products (together abbreviated PPCPs) and endocrine-disrupting substances (EDSs). The term *emerging contaminants* for this group of substances is borrowed from the U.S. Geological Survey and refers to the fact that these recently-detected pollutants have not been part of standard water quality testing programs.

The **Preface** describes the typical development of an environmental issue, observing that that of emerging contaminants is only at an early stage, namely Investigation. Its implications are sufficiently far-reaching that it would nevertheless be timely for water policy analysts and decision-makers to begin to incorporate the issue into their thinking.



As described in the **Introduction**, the report is organized around Environment Canada's approach to state of the environment indicators. These provide four separate clusters of linked information, starting with some human activity that creates a changed environmental condition. This information about what is happening in the environment is connected in turn to its ecological, health, social and economic impacts. The final information cluster describes the societal responses intended to modify or curtail the human activity in question. These four groups of information are addressed in this report's Sections 2, 3, 4, and 5 respectively. However, the document emphasizes that at this time, much remains unclear or unknown.

Section 2 considers one part of the causative human activity which is reasonably well understood, namely pharmaceutical use and its enormous increase in the past half century. For example, in 2004 in the United States, almost half of all Americans were taking one prescription drug. Five out of six people 65 years and older were taking at least one drug, and half of that age group three or more medications. There, the rate of antibiotic use averaged one prescription per capita per year (in Canada, it is 0.8 prescriptions/person/year). Between July 2001 and August 2002, there were 326.2 million human medical prescriptions filled in Canada.



The use of drugs in veterinary medicine, farming practices, and aquaculture has also grown.

Not only are drugs used for therapeutic purposes, but hormones and sub-therapeutic doses of antibiotics are used in animals as growth promoters. Antibiotics also are often added to animal feed for disease prevention. In the United States, the Union of Concerned Scientists estimates that 70% of all antibiotic production is given to pigs, cows, and chickens. Some 25 million pounds of antibiotics and other drugs are given to U.S. farm animals, more than eight times the three million pounds used to treat human disease. This non-therapeutic use of antibiotics has increased one and a half times between 1985 and 2001. As well, two thirds of beef cattle for American consumers are given growth hormones in feed or ear implants; these are also widely administered in Canadian beef operations. U.S. dairy cattle can also be fed bovine growth hormone (rBGH) to increase milk production (this is prohibited in Canada).

Section 3 reviews how emerging contaminants get into water and what happens to them. The following are the four main routes:
(1) substances used in manufacturing are discharged into wastewater;
(2) unused medications and cleansers and personal care products like shampoos are discarded into or washed away with wastewater;
(3) drugs and their metabolites as well as bioactive substances like caffeine are excreted in the user's urine and feces and enter the wastewater stream directly; and
(4) discarded or excreted substances are carried in run-off from private septic systems, treatment facilities for livestock waste and aquaculture operations, and from animal waste and sewage sludge spread on farm fields. In humans, between 50 - 90% of the active ingredients in drugs are not absorbed and are excreted. The figures are similar in other animals, and for antibiotics, widely used in animal feed, some 25 - 75% of the drugs pass into the environment. Consequently, major points of concentration are immediately downstream from manufacturing plant outfalls, sewage treatment facilities, livestock operations, and in leachate from septic systems.

Testing for emerging contaminants in water only began in the later 1990s, and the first international conference reviewing results was held in 2000. Much of the testing has been in Europe and the United States. One of the most extensive surveillance programs has been conducted by the U.S. Geological Survey since 1999, and has tested for more than 150 compounds in surface water, groundwater, and streambed sediments all over the United States. Emerging contaminants have been found virtually everywhere. For instance, in one sampling program of source water in 25 groundwater and 49 surface water supplies, at least one of the 124 chemicals tested for was found in 96% of the samples, with most sites having a number of different contaminants present. Testing in Canada has been much more limited, with one study of samples near sewage treatment plants in 14 Canadian cities finding a number of pharmaceutical products present, though it must be emphasized that concentrations found are very low, ranging in the micrograms per litre down to nanograms per litre range.

The physical fate of these contaminants varies greatly, depending on the substance. Many are removed by wastewater treatment; but some, like nonylphenol, simply partition to sewage sludge. Some are removed by streambank filtration or attach to sediments, some are volatilized from

water, some are degraded by light and by biological or chemical processes, and some are taken up by plants and animals. However, some contaminants are persistent, even surviving drinking water treatment. The insect repellent DEET and the anticonvulsant drug carbamazepine were noted by a Minnesota study as being of particular concern because they are both persistent and readily transported in water. An American survey of more than 100 compounds in a drinking water treatment plant found 22 persisted in treated water (though again, at extremely low concentrations, far below amounts found in even one pill). A journalistic investigation in Canada in 2003 looked at tap water from 10 Canadian cities and found low concentrations of pharmaceutical products in four samples, including carbamazepine and the cholesterol drug gemfibrozil; a more recent study of acidic pharmaceutical products in 22 southern Ontario drinking water treatment plants by the National Water Research Institute found very low levels of eight different drugs, including gemfibrozil, the painkillers ibuprofen and naproxen, and the antimicrobial triclosan present.

Section 4 considers the ecological impacts, including human health effects, of these emerging contaminants. There are two important **known** effects, though there may be others, particularly of sub-therapeutic doses of drugs not clearly linked to endocrine disruption.

One is connected to an important subset of pharmaceutical products, namely antibiotics or antimicrobials. As discussed in detail in Appendix A, the use and presence of these drugs can lead to drug-resistant strains of pathogens; the development of resistance in previously susceptible strains of bacteria is known as antimicrobial resistance, or AMR. However, the very low concentrations of antibiotics found in surface or drinking water probably do not cause the development of AMR specifically from those drug residues in that water. Concerns regarding AMR in the environment relate to finding resistant genes or bacteria in soil and water, but the source in water is likely from fecally contaminated water or agricultural runoff. However, there are unresolved questions about the significance of residues of antibiotics in groundwater and urban wastewater which are being investigated, such as the possible role of wastewater treatment plants in maintaining or encouraging AMR.

The second set of impacts is related to a different set of chemicals whose effects are to disrupt the endocrine systems of living organisms. The endocrine glands produce chemical messengers, called hormones, which are transported to various sites in the body through the bloodstream; these hormones direct and control many of the body's functions, including growth, development, and reproduction. Endocrine-disrupting substances or compounds (EDSs or EDCs) can mimic or block the action of natural hormones, or otherwise interfere with hormone production, release, transport, metabolism, or elimination. They include pharmaceuticals such as birth control pills and synthetic hormones. Other products also incorporate or are themselves EDSs: industrial chemicals such as PCBs, metals, and plasicizers; various surfactants, fragrances, and preservatives in cleaning and personal care products; contaminants like dioxins; and pesticides, including the insect repellent DEET. In humans and other large mammals their health effects are not well understood. In fish, birds, and other wildlife, effects have included reproductive impairment or

failure, deformities, and feminization.

The report discusses the history of the developing focus on EDSs, including some early warnings about specific chemicals (for example, in 1971, discovering unusual cancers in the daughters of pregnant women who took the synthetic estrogen diethylstilbestrol [DES]; in the late 1980s, identifying the compound p-nonylphenol that was leaching in minute quantities from tubes used in medical research studies and was mimicking estrogen in its effects on cell cultures).

Much of the scientific work on EDSs has linked effects on fish and wildlife with exposure to EDSs in water. Examples include impaired reproduction of fish exposed to pulp and paper mill effluent; abnormal reproduction in snails exposed to anti-fouling chemicals used on ship hulls; depressed thyroid and immune function in fish-eating birds; and feminization of fish near municipal sewage effluent outfalls, a finding that has been replicated in many studies. A study in 2003 in the Experimental Lakes area of Ontario added the estrogen 17-ethynylestradiol to a pristine lake in an average concentration of 5 - 6 nanograms per litre, similar to levels found downstream from wastewater treatment plants. In that time span the scientists did not find changes in the lower levels of the food chain, but the fathead minnow population collapsed entirely.

Such research is very suggestive, but cannot tell us with certainty about effects on people. Many more animal studies, along with clinical research and statistical trends and patterns will be needed before there is a widely accepted consensus about human health impacts. A confusing factor in research related to specifically to estrogen and estrogen-mimicking compounds in the environment is that humans and other animals produce and excrete estrogen naturally, and some (phytoestrogens) are even produced by plants. Estrogen has, however, been linked to certain cancers in many studies.

Some of the suggestive evidence connecting human health effects with possible exposure to EDSs somewhere in the environment is the change in the incidence of disease and abnormalities related to the endocrine system. Noteworthy in this context is the recent rise in the incidence of breast, testicular, and prostate cancers at a time when overall cancer rates are declining. For example, in Ontario, the testicular cancer incidence rose about 60 per cent in the late 1990s, with the fastest increase in the youngest age group.

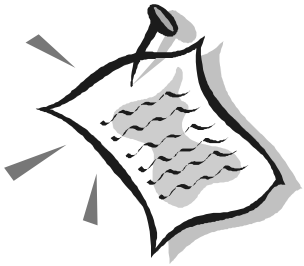
Section 5 reviews a wide range of societal responses to pharmaceuticals and other emerging contaminants. It is noted that governments have already regulated a number of these contaminants, such as pesticides, because of toxicity, persistence, or bioaccumulation, but without placing them in the context of emerging contaminants.

A number of governments, including Canada, the United States, and the European Union have begun initiatives to investigate and determine what to do about the hazards and risks

of AMR and EDSs. For AMR, one major category of responses involves various changes in medical practice; however, this document focuses only on environment-related efforts. These include surveillance, education, and reductions in antibiotic use in animals, particularly for growth promotion and prophylactic uses, and in restricting products used in human therapy.

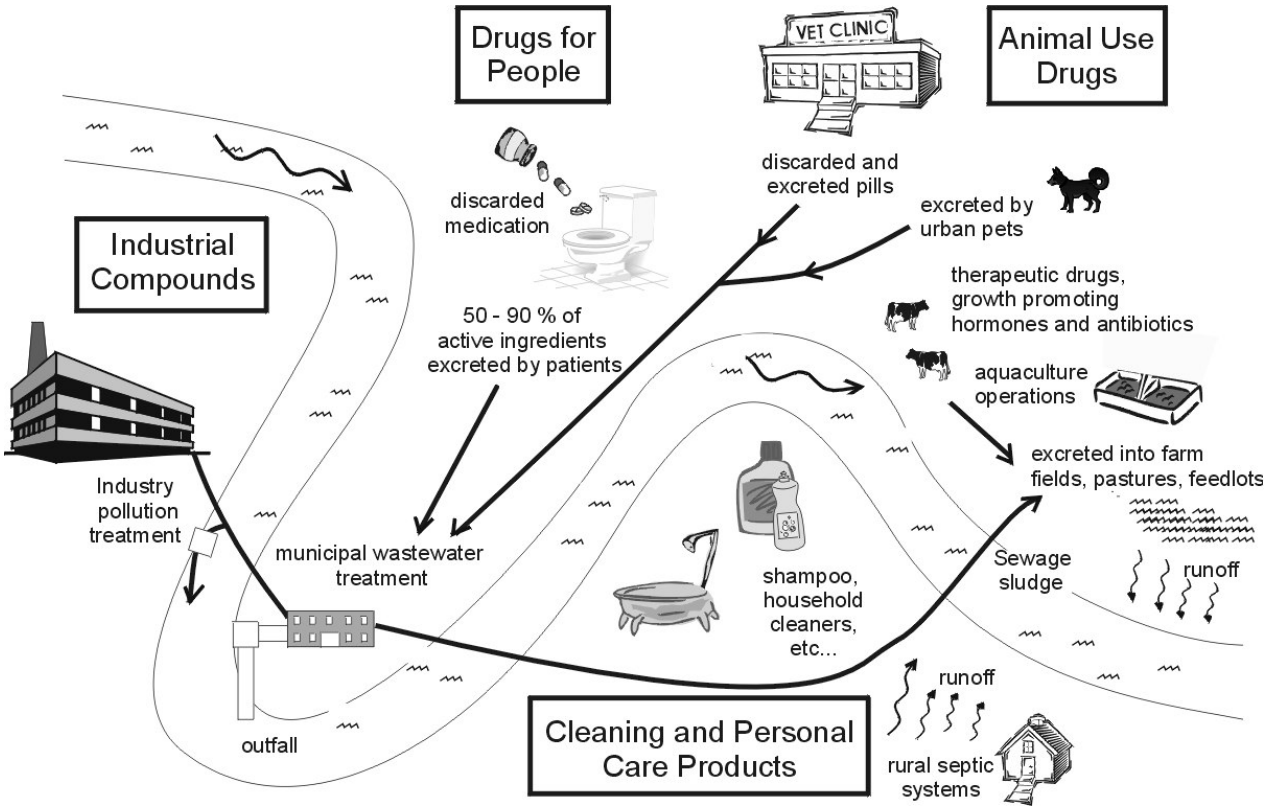
For EDSs, the problem begins with the fact that there is not yet even a comprehensive identification of all these substances or their effects. Mapping out the problem scientifically is clearly the most important task at this stage. One approach that may be used in identifying priority substances is currently being finalized by the European Medicines Agency (EMEA) for a guidance document for testing new pharmaceutical products. It first involves a rough calculation of the ratio of the compound's predicted environmental concentration (PEC) to its predicted "no effects" concentration (PNEC), i.e., the PEC/PNEC ratio. If the PEC is greater than the PNEC, it would require the submission of data from a number of tests for chronic environmental toxicity.

In general, it is better and cheaper environmental policy to restrict potential pollutants at the earliest possible stage. For some substances, this means not using them in the first place, or at least curtailing the amounts used. However, we are a long way from having enough scientific information to develop legislation and regulations, especially for EDSs, and research is the most vital need overall. Public education, advocacy, and consumer choice; municipal by-laws about avoiding home pesticide use and not discarding drugs down toilets and sewers; pharmaceutical take-back programs such as a province-wide initiative in British Columbia; and labeling could all play a role in reducing the scale of potential problems from these contaminants. However, because many human-use drugs are medically important and are excreted by people we will also need to rely on wastewater and drinking water treatment (as well as natural processes) to provide barriers to the presence of pharmaceuticals in water. (This will probably apply to some important uses of certain industrial chemicals as well.) More research by governments and also the private sector on appropriate water treatment technologies, sludge handling, and safe disposal would therefore be helpful.



In **Section 6**, the document concludes by noting that we do not yet have enough information even to develop a strategy that can effectively weight various actions related to emerging contaminants. At this point, the best approach is to encourage individuals and all sectors of society to find ways that they can contribute to this and other issues by moving as far as possible toward a culture of environmental stewardship. The report concludes with 11 general recommendations that apply to many different actors in society.

Diagram 1: Origins of Emerging Contaminants Detected in Water
(over 150 substances)



Recommendations

1. Consult and develop a process to determine priority endocrine disruptors in sewage and industrial effluents and review licensing of pharmaceuticals and other chemicals as well as effluent permits in that context.

2. Significantly increase research efforts and funding for science related to these issues, including surveillance and monitoring, environmental risks, ecological science, and human and wildlife health.

3. Increase research on municipal water treatment technologies that better remove pharmaceuticals and related compounds, and provide ongoing information on such technologies for municipalities. Develop related information programs as part of municipal infrastructure support programs.

4. Phase out use of antibiotics and of hormones as animal growth promoters and review the use of preventive antibiotics in animal feed for eventual phase out. Immediately prohibit human use classes of antibiotics for growth promotion and routine prophylactic uses in poultry and livestock operations.

5. Review sewage sludge and animal manure management practices in light of issues related to pharmaceuticals and resistant bacteria in water.

6. Support (and/or practice) organic agricultural production; in particular, organic or at least "natural" meat, fish, and dairy products (or eat vegetarian alternatives).

7. For personal care and cleaning products, as an interim measure increase

public education now through an environmental labeling program and/or identification of products free of both suspected endocrine disruptors and antimicrobial substances linked to antibiotic resistance. As more information is acquired, ban problematic ingredients.

8. Support or develop province-wide product stewardship programs for return of unused drugs.

9. Support or develop municipal by-laws banning pharmaceuticals and other chemical discards in sewers and restricting pesticide use; ensure enforcement capability and action.

10. Increase support for public education and awareness programs on these issues and leadership to develop action initiatives.

11. Identify stakeholders and initiate public discussion and multi-stakeholder consultation in prioritizing government actions, problem areas, and what to do about both.

Preface: The Life Cycle of Environmental Issues

Like humans and other living things, environmental issues have a life cycle. Typically there are five stages in the environmental issues cycle, with different sets of people playing the main roles at each stage.

In the first stage, **Observation**, the main actors are the people who first notice that something's amiss. They may be scientists or perhaps anglers, birders, farmers, or hunters, but they are acute observers with enough knowledge to recognize that something unusual is happening to some part of the environment.

The second stage is **Investigation**. Scientists, though usually only a small number, play the key role here, beginning to investigate these observations systematically and developing hypotheses to explain what they see happening. Some begin to be alarmed by what they find or suspect. The first professional conferences on the topic are organized and articles in scientific journals begin to be published.

The third stage, **Analysis, Advocacy and Argument**, adds to the number of players. Environmental groups (or ENGOs – environmental non-government organizations) are especially important in alerting the mainstream media, who begin to report on the problem to the larger public, some of whom start demanding that action be taken. More scientists and academics, business and industry groups, government agencies and regulators, and politicians, along with those specifically affected, such as labour unions or homeowners' associations, become engaged. Although its causes become clearer, there is lively and sometimes acrimonious debate about the significance of the problem and especially about proposed courses of action to address it. In this phase, the focus tends to shift from the natural environment and its components to the impacts of controlling the human activities implicated in the issue.

After sometimes lengthy public debate, the fourth stage, **Decisions and Action**, is reached. Regulatory agencies and political decision-makers with their advisors consider in detail the

political, economic, and environmental consequences of various options and decide what specific public actions, such as passing new legislation, they will take. However, this stage is spread out further than simply being the point when the major public approaches are finally determined. Individuals and some progressive companies may already have been initiating changes in their own actions for some time. Different agencies and political jurisdictions will probably be involved, and, for various reasons, some may act much more slowly than others. And even for the most significant legally mandated changes, the necessary budgeting, acquisition of new technology, and new institutional arrangements and information systems require a considerable start-up period.

The fifth and final stage is **Feedback and Revision**. Monitoring of both the environmental conditions and the actions taken to address the problem may reveal the need for stronger (or, conceivably, less stringent) regulatory requirements, more policing, or even a completely revised approach, with further iterations of the process of analysis, debate, decision making and review.

* * * * * * *

In this report, intended for general readers with an interest in the environment, we discuss the emerging issues of pharmaceuticals and related chemicals now being detected in water. We borrow the term *emerging contaminants* from the U.S. Geological Survey to refer to these pharmaceuticals, personal care products, and endocrine-disrupting substances; as we will discuss, the basis for the category grouping is simply potentially toxic pollutants now being identified that previously had not been routinely tested for in water. These contaminants make for an untidy description of the issues, since they share neither a basic chemistry, nor a single ecological or health impact, nor do they come from just one category of products. We emphasize here some of the basic science and the history of related health and toxic chemical issues in order to provide non-scientist readers with background and contextual information to which they can refer as various aspects of these topics evolve over time. (Readers can, of course, skip sections of the document that provide more detail than they need at the moment, and concentrate on acquainting themselves generally with the material.) In some ways, it may seem premature to attempt any summarizing report at this time, because the stage of the issue where we are now is best characterized, from the above discussion, as ***Investigative***. The extent, the precise nature, and certainly the significance of the actual and potential problems these substances create by their presence in the environment are not well understood. And there has so far been little public awareness or discussion of the broad issues in a comprehensive way, and even fewer proposals about what can or should be done.

Nevertheless, because of the tremendously widespread, and increasing, use of pharmaceutical

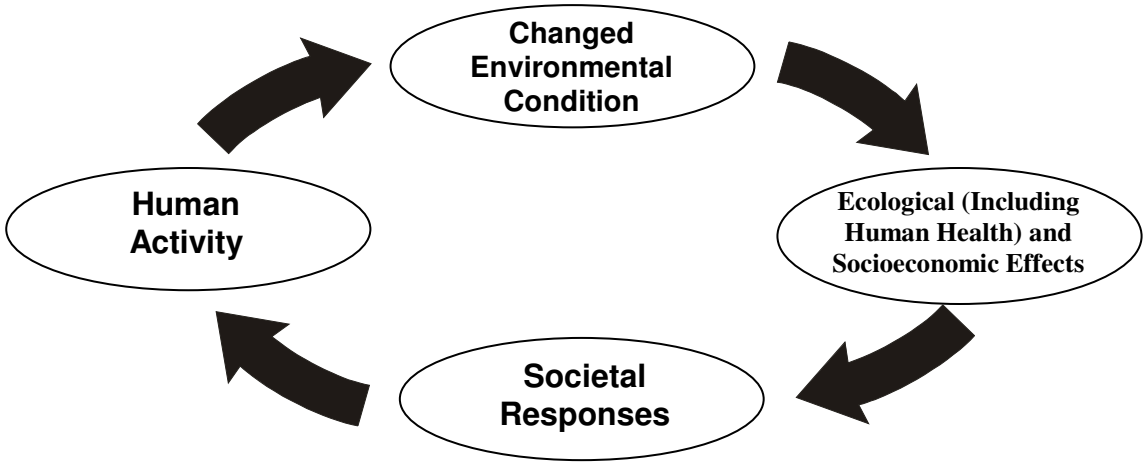
products, as well as of similarly bioactive substances, CIELAP believes that the potential concerns are so large in scale, and the prudent modifications to human activities so demanding institutionally that it is worthwhile, even at this early stage, to begin the discussion.

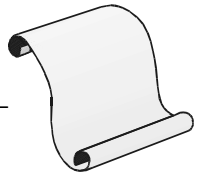
It is also timely in that both the quality and the quantity of water in Canada are increasingly, and for good reason, a matter of public policy reviews. The Walkerton, Ontario water tragedy, where people died and hundreds more were sickened from bacterially-contaminated municipal water, the cryptosporidiosis outbreak in North Battleford, Saskatchewan, also from a poorly operated, aging, and inadequately regulated municipal treatment plant, and climate instability caused by the ongoing buildup of greenhouse gases in Earth's atmosphere, increasing the likelihood both of droughts and extreme weather events, are cause for a renewed interest in water planning and policy. In matters of health, safety, and the environment, investing time in anticipating, planning, and improving coordination is necessary for coping with the unexpected – which, we should recognize, is always to be expected. Considering the implications of these emerging contaminants in the context of a fresh look at water policies and water infrastructure would be a positive step in coordinated, adaptive management.

1. Introduction: Presenting the State of the Debate

To report on the state of the environment, we basically need to know *what* is happening, *why* it is happening, why it's *important*, and *what's being done about it.* In its work on indicators, Environment Canada has often used a graphic model, a version of which is shown in **Diagram 2**, to show the dynamics of an environmental issue. This model links a changed environmental condition (i.e., what is happening) with the human activity which causes that change (why it is happening). The change in environmental conditions in turn has ecological and socio-economic effects (why the change matters), and these can result in a response by society to control or modify its activities (what's being done about the environmental change).

Diagram 2: Environmental Linkages - Graphics adapted from Environment Canada's State of the Environment Reporting Program for Environmental Indicators





This model illustrates a systems approach to environmental problems, letting us see at a glance what key information is required to understand the status of the problem. When the environmental conditions, the human causes, and the ecological and other consequences have been well investigated and are adequately understood and documented, and society is acting to modify the human (or *anthropogenic*) causes, information from one or more of these groups can be used to develop environmental indicators. These can be tracked over time, allowing us to assess ongoing progress on the issue, or the lack of it, with some confidence.

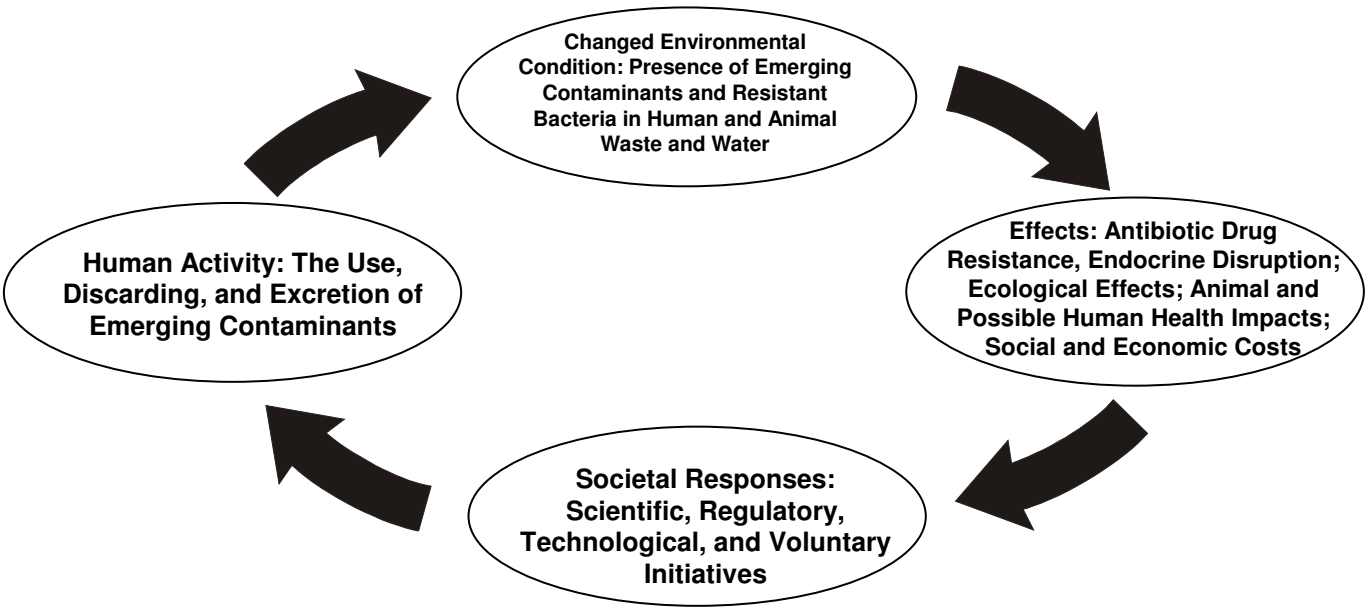
But as we noted in the Preface, in the case of emerging contaminants in water, the status of virtually none of these four clusters of vital information is fully in focus. To begin with, much of the research material that presents the issue groups together pharmaceuticals and personal care products, usually labeled *PPCPs*, along with various industrial and other chemicals that are suspected endocrine-disrupting substances *(EDSs*). This categorization is related more to new surveillance programs using today's improved water testing capabilities, whereby it is now possible to identify minute quantities of many previously undetectable chemicals, than it is to looking at one specific type of product or one specific effect.[a] Consequently, although pharmaceuticals are a major target of investigation, depending on the context other substances may also be part of the same discussion.

Even more important, the relationships linking causes and consequences are difficult to pin down. In particular, a clear understanding of the full range of ecological effects from the presence of these substances in the environment, including the significance for human health, is far from having been established, though the potential implications could be far-reaching.

Nevertheless, only a systems model of the issue provides the kind of overview that allows us to think strategically about what is known, unknown, and needs to be known, and to consider all possible points of intervention in deciding what responses should be undertaken. We will use this model, therefore, as the basis for reviewing the issues related to what we know about pharmaceuticals and other emerging contaminants in water and for analyzing what could be done about the known and suspected problems. **Diagram 3** shows the linkages for these aspects of the issue.

[a] For instance, one of the most important venues where scientific research on these issues is presented is the series of international conferences on pharmaceuticals and endocrine-disrupting substances in water held since 2000 by the National Groundwater Association in the United States. Pharmaceuticals, personal care products, and other chemicals are discussed there, as well as both antibiotic resistance and endocrine disruption.

Diagram 3: Emerging Contaminants in Water: Relationships, Information, and Issues



We use as the starting point for the report something we *are* sure of, namely the proliferation of pharmaceuticals in Canada and the United States in particular. In terms of the systems model described above, the increasing quantity of pharmaceuticals entering the environment through various routes is one crucial part of the human activities and the changed environmental conditions about which we are concerned. The situation can also be fairly readily quantified. Today's growing pharmaceutical use is thus treated here as an indicator or the prime example of the problematic human activity related to these new contaminants found in water, although other chemicals and products are also implicated.

Scientists are only in the beginning stages of investigating many aspects of questions related to emerging contaminants, so we will detail the chronology of observations that triggered disquiet and the development of these stories to date in presenting information about ecological and health effects, underlining why it is urgent to find out more. Finally, we will consider society's responses: what's been done so far, what questions still need to be asked and answered from a public policy perspective, and what might be some of the options and choices for dealing responsibly with pharmaceuticals and other emerging contaminants in light of a precautionary approach.

2. The Rise of Legal Drug Use

The United States may have declared a "war on drugs," but in that country as in most of the industrialized world, that "war" is strictly about illegal substances. The legal use of drugs has ballooned in the past several decades.

Pharmaceuticals or drugs, usually defined as "chemical substances which alter the physiological state of living organisms,"[b] are playing an increasingly important role, not only in human medicine, but also in veterinary medicine, aquaculture, and for disease prevention and as growth promoters in animal husbandry.

2.1 Medical Drug Use in North America

In the United States, spending for prescription drugs was (US)$179.2 billion in 2003, four times larger than it was in 1990, comprising nearly 11% of national health care dollars and growing faster than any other components of that spending.[1] And an American study, *Health, United States, 2004*, released by the National Center for Health Statistics in December, 2004, stated that prescription drug use is rising among all ages, with almost half of all Americans taking at least one prescription drug, one in six taking three or more drugs, and five out of six people 65 years old and up taking at least one drug and half of that age group three or more medications. The same study noted that, between the 1988-94 period and 1999-2000, the proportion of people taking at least one drug has increased 13%,

[b]This definition from the *Oxford Concise Science Dictionary, Third Edition* (Oxford: Oxford University Press, 1996)

while in the same interval there has been a 40% increase in the proportion of people taking three or more medications. In the United States the drugs whose use is growing especially quickly are non-steroidal anti-inflammatory drugs; anti-depressants; blood glucose/sugar regulators; and cholesterol-lowering statins.[2] Prescriptions for antibiotics, one of the most frequently used types of drugs, have decreased slightly in recent years, but in the United States the rate still averages one prescription of antibiotics per capita per year (the rate in Canada is 0.8 prescriptions/person/year).[3]

The overall situation is similar in Canada. Pharmaceutical drug expenditures in Canada in 2002 were (Cn)$18.4 billion, the second largest category of health care spending next to hospital services. In 1985, therapeutic drugs accounted for 9.5% of Canadian health care dollars; that proportion had risen to a forecast 16.3% in 2003.[4] Between July 2001 and August 2002, there were 326.2 million human medical prescriptions filled in Canada; the top five categories here were cardiovasculars such as Altace; psychotherapeutics like the antidepressant Paxil; hormones, such as Premarin, used in hormone replacement therapy; and systemic anti-infectives.[5]

2.2 Drugs in Veterinary Medicine, Farming Practices and Aquaculture

Not all pharmaceutical products are used for people. Health Canada's Drug Products Database lists all the drug products marketed in Canada; these include disinfectants and veterinary medications as well as products used in human medicine. Those database product listings have increased from about 17,000 in 1987 to over 24,000 in 2004, of which more than 2500 are approved veterinary products.

Veterinary medications are, of course, used to prevent or treat illness; many diseases and conditions of other animals are similar to those in humans, and, especially for companion animals, drugs are increasingly being used to extend treatment to animals that a generation ago might not have been treated or even been euthanized for conditions like anxiety and behavioural problems, arthritis, and cancer. Since there are relatively few drugs developed solely for veterinary use, veterinarians can also prescribe human drugs for these purposes, a practice called *extra-label* or *off-label use*. In general, pharmaceuticals used for non-human animals can be found in all the same 15 or so categories of drugs[c] as those for human use. There are also specific health

[c] Drugs have three names – their chemical name, brand name, and generic name – but they are usually categorized by what they do or treat. Categories can vary, but the following is a typical broad categorization from a study guide for the pharmacology test for nursing licensure: anti-infective agents; antineoplastic agents (treat malignancies); cardiovascular agents; fluid and electrolytic agents; gastrointestinal tract agents; hematologic agents (blood and clotting disorders);

conditions and products for particular species, such as vaccines for diseases like feline leukemia and oral medications for dogs and cats used against fleas and ticks. There are about 5 million dogs, 7 million cats and under a million horses in Canada, and over 65 million owned dogs, 77 million cats and more than 9 million horses in the United States; it is now the norm for owners to employ veterinary care for routine health monitoring as well as accidents and illness, and as with humans, drug use has increased.

For farm animals, however, the biggest part of pharmaceutical use is not for therapeutic purposes, but rather for disease prevention, especially in crowded conditions such as cattle feedlots, and for growth promotion. In 1949, it was discovered that sub-therapeutic doses of antibiotics caused chickens to grow significantly faster than they otherwise would, although the precise mechanism was not clear.[6] Since that time, it has become routine to put antibiotics in animal feed. In a 2003 study, the Union of Concerned Scientists estimated that 70% of all antibiotics production in the United States is given to farm animals, specifically pigs, cows, and chickens.[7] Some agro-industry estimates put the percentage as considerably lower, but it is nonetheless substantial.

In the United States, about 25 million pounds of antibiotics and related drugs are administered to animals for non-therapeutic purposes, more than eight times the 3 million pounds used to treat human disease. This non-therapeutic use of antibiotics has increased one and a half times between 1985 and 2001. It is estimated that 25 - 75% of the antibiotics administered to animals (including humans) pass into the environment through their urine and manure.[8]

As well as antibiotics, hormones to promote growth are given to cattle, in feed or as ear implants (growth-promoting hormones are not allowed to be given to poultry and hogs in either Canada or the United States, and the European Union bans their use in cattle as well). Two thirds of beef cattle for American consumers (24 million cows of 36 million) are given growth hormones; of feedlot cattle in the United States, about 90% are hormone implanted.[9] In Canada, Health Canada, under the Food and Drug Act, has approved six growth-promoting hormones;[d] these are widely

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hormonal agents; immunomodulation agents; autonomic nervous system agents; central nervous system agents; nutritional agents; ophthalmic, otic, and nasal agents (eye, ear, nose and throat treatments); respiratory tract agents; topical agents (skin or hair applications); and miscellaneous medications. Each of these categories is usually subdivided into more specific classes; for example, anti-infective agents include, among others, antivirals; penicillins; quinolones; macrolides; and tetracyclines (from *Pharmacology Made Easy for NCLEX-PN* by Linda Waide and Berta Roland. Chicago: Chicago Review Press Incorporated, 2001).

[d]These include the natural hormones 17 beta-estradiol, progesterone, and testosterone; and the synthetic hormones zeramol, trenbolone acetate, and melangestrol acetate. Diethyl stilbesterol

used here in commercial beef production. (Though the number of cattle being given extra hormones is very large, it should be pointed out that the non-synthetic versions of these growth hormones are also produced naturally in both plants and animals.) In the United States, dairy cows can also be fed recombinant bovine growth hormone (rBGH) to increase milk production, but Canada has banned its use since 1999, mainly because of concerns about animal health and welfare.

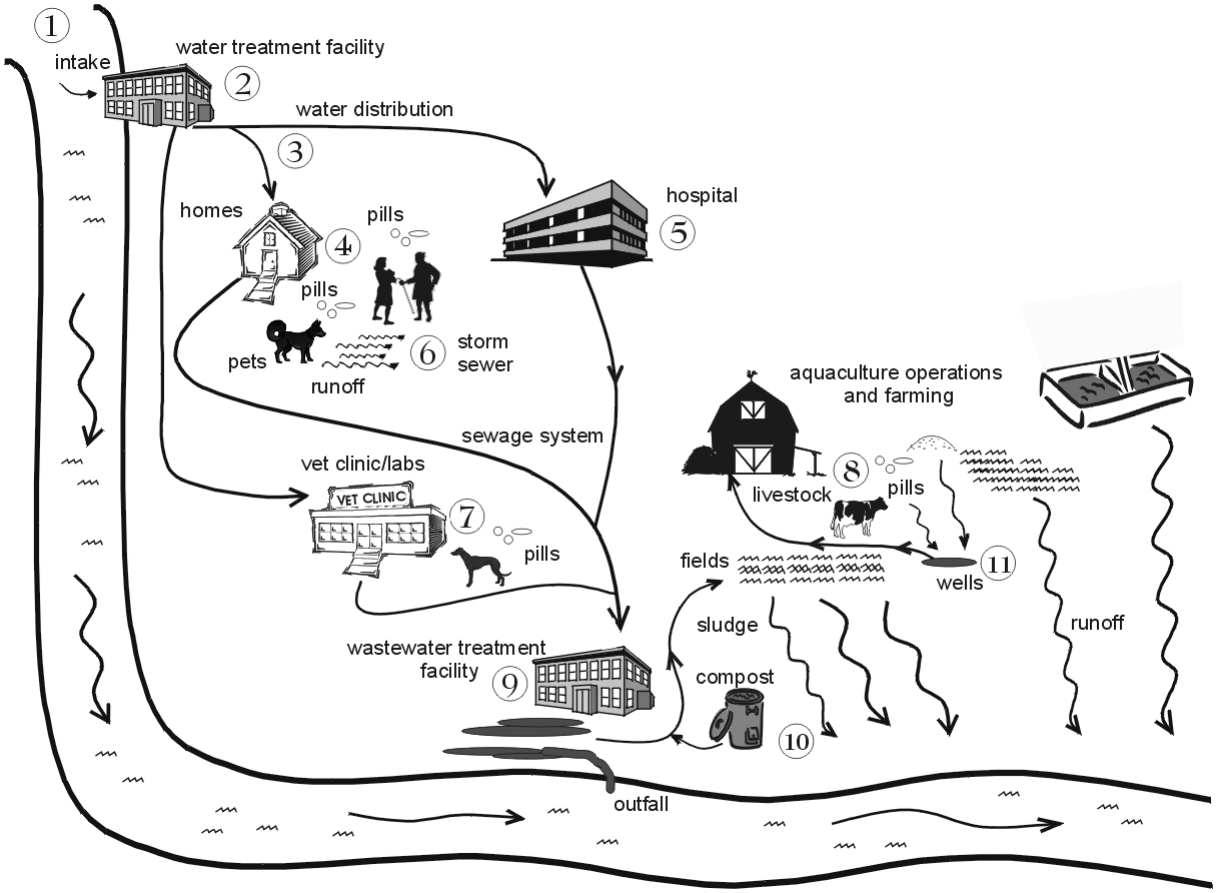
In the growing aquaculture industry, various pharmaceutical products are also widely used. These include disinfection agents; antibiotics for disease prevention and therapy; and hormones for control of spawning and for growth promotion by sex selection, since either males or females of certain species grow larger than the opposite sex. According to a paper published on Canada's Fisheries and Oceans website,[10] seven chemicals are approved for sale in Canada when labelled for food fish use. These include one anesthetic, two fungicides/disinfectants, and four antibiotics.[e]

(DES) is prohibited in Canada.

[e] The antibiotics are oxytetracycline; florfenicol; sulfadimethoxine plus ormetoprim; and sulfadiazine plus trimethoprim; the fungicides/disinfectants are formaldehyde and hydrogen peroxide.

3. How Pharmaceuticals, Personal Care Products and Other Emerging Contaminants Get into Water and What Happens to Them

Diagram 4: How Pharmaceuticals Get Into Water



① **Water Source** (surface)

② **Municipal water treatment facility** - treatment a barrier to some pharmaceuticals

③ **Municipal water distribution system**

④ **Domestic waste** - pharmaceutical metabolites enter wastewater system

⑤ **Hospital waste** from patients, hospital labs, and pharmacies - both metabolites and pharmaceuticals enter waste water system

⑥ **Pets** treated with medication produce waste – metabolites runoff to storm sewers

⑦ **Vet clinics, hospitals, pharmacies, and labs produce waste** – metabolites and discarded pharmaceuticals enter sewers

⑧ **Farms** discard drugs into wastewater and metabolites from treated animals go into runoff

⑨ **Sewage treatment plant** destroys some, but not all, pharmaceuticals and metabolites - some discharged into sourcewater; sludge often spread on fields, ultimately resulting in runoff to sourcewater.

⑩ **Municipal compost** often spread on fields; metabolites from animal waste, and also from diapers, may be present

⑪ **Municipal** – town groundwater sources and rural wells receive runoff with metabolites from farm animals

* * * * * * *

Basically, there are four major theoretical routes that bring pharmaceuticals, personal care products, and some other emerging contaminants into water.

· *Manufacturing facilities*. Substances used in the manufacture of pharmaceuticals and other products may be discharged with wastewater from the plant.

· *User discards into treated wastewater*. Unused medications such as from old, partially used prescriptions or ones that are past their expiration date may be discarded into wastewater from homes, businesses, hospitals and clinics, pharmacies, and veterinary practices. Other contaminants found in cleaning and personal care products like shampoos and insect repellants are discarded into or washed away with wastewater.

· *Excretions into treated wastewater*. Drugs or their metabolites (the substances they become after being taken into the body and metabolized) as well as bioactive substances like caffeine and nicotine metabolites are excreted in the user's urine and feces and thus enter the wastewater stream directly from homes, businesses, schools, hospitals and other

institutions hooked up through the sewer system to central wastewater treatment facilities. In humans, between 50-90% of the active ingredients in drugs typically are not absorbed and are excreted.[11] Other animals also excrete significant quantities of the drugs they are given.

· *Discards and excretions into runoff flowing to water bodies or groundwater*. Discarded or excreted substances may be carried in the runoff from private septic systems or treatment facilities for livestock waste or aquaculture operations, or in runoff from manure or sewage sludge spread on farm fields, leachate from landfills, and in storm sewer runoff that carries pet or human waste.

The most obvious points of concentration are immediately downstream from the wastewater outfalls of manufacturing plants, sewage treatment facilities, livestock operations, and leachate from private septic systems. The question is whether these emerging contaminants are actually being documented from these possible sources, and to answer that, someone has to look. Now that researchers have begun to do just that, there is mounting evidence that the answer is yes, the presence of these chemicals in water is widespread, although the concentrations found are minute, often a thousand to a million times lower than human therapeutic doses of drugs.

3.1 Testing for Pharmaceuticals and Other Emerging Contaminants in Water

The first international scientific conference specifically on this subject was only held in 2000. By the fall of 2004, at the (United States-based) National Groundwater Association's 4th International Conference on Pharmaceuticals and Endocrine Disrupting Chemicals in Water in Minneapolis, there were more than 60 scientific papers presented, discussing the nearly ubiquitous presence and the fate of these substances in rivers, lakes, and groundwater in various locations all over the United States, in Germany, Great Britain, Israel, and the Philippines. Papers presented at that conference indicated that pharmaceuticals and other emerging contaminants were found everywhere in both surface and groundwater, though more widely in surface water bodies; in central wastewater treatment facility effluent; in biosolids (sewage sludge); in landfill leachate plumes; in effluent from on-site treatment systems; in manure lagoons in poultry and swine operations and in water from fish hatcheries; in effluent from private home septic systems, with reduced but still detectible quantities after the percolation field ; and in effluent plumes originating from hospitals and veterinary uses. As well, as we will discuss Section 3.2, these substances have been found in domestic tap water.

To date, much of this work on water testing has been done in Europe, especially in Germany through the Technical University of Berlin and the Federal Institute of Risk Assessment, and in the United States. For example, the New York State Department of Health has surveyed the entire New York City watershed that supplies that city's drinking water for 11 pharmaceutical and bioactive substances; at sites west of the Hudson River, five drugs were not present, but caffeine was found at half the sites and ibuprofen and the blood pressure drug atenolol were detected in all samples.[12]

One of the most extensive research programs is the Emerging Chemical Contaminants Project of the United States Geological Survey (USGS), which is part of their Toxic Substances Hydrology Program. Since 1999, the USGS has been investigating the presence of what they refer to as "emerging contaminants" in water.[13] "Emerging contaminants" are defined in this context as substances not normally tested for in water quality sampling. Along with pharmaceuticals, they include a number of industrial chemicals, particularly suspected EDSs, that are used in plastics, cleaning agents, personal care products like shampoos, and pesticides. In this program, the USGS has surveyed:

· Streambed sediments in 12 states and found many contaminated;

· 139 streams in 30 states, with emerging contaminants found in 80% of the streams, and with half having 7 chemicals and a third with 10 or more present;

· Source water from 25 groundwater and 49 surface water supplies for 124 emerging contaminants with contamination from at least one chemical found in 96% of the samples;

· Groundwater from 47 sites in 18 states tested for 83 emerging contaminants, with 98% having at least one contaminant, and 46% of those chemicals showing up more than once.

Much less testing has been done in Canada. However, in October, 2002, CTV obtained and published the results of a study funded in part by Environment Canada and conducted by scientists from Trent University. Researchers tested water samples near sewage treatment plants in 14 Canadian cities and in open water in the Great Lakes. Pharmaceutical products such as antibiotics, anti-inflammatories, drugs used to treat high blood pressure and epilepsy and birth control hormones were found in the samples, ranging in concentration from very low to even higher than similar samples in Europe.[14] This was described as the first such study in Canada, and to date, no other major sampling program for pharmaceuticals in the environment has been done here. It is reasonable to assume, however, that pharmaceuticals and other emerging contaminants are widely present in the streams, lakes, rivers, and groundwater in the densely populated regions of the country. It should be noted, though, that the concentrations of pharmaceuticals found in water

have been extremely low compared to therapeutic doses, generally in the range of micrograms/litre down to nanograms/litre. For most drugs, usually prescribed in doses ranging from several to several hundred milligrams, a person would have to drink thousands or even millions of litres of surface water to ingest an amount comparable to that in one pill.

3.2 The Fate of Pharmaceuticals and Other Emerging Contaminants in Water and the Environment

Research into the environmental fate of pharmaceuticals and many of the other emerging contaminants is made somewhat more complex by the fact that their use is so common that there is a virtually continuous supply entering the environment. Especially in Europe and parts of the United States, the flows of the lower stretches of many rivers consist partly or, sometimes, entirely of treated effluent, with each wastewater treatment facility adding its contribution to the loading of pharmaceutical and other contaminants.

Seasonal flow conditions in rivers and streams usually vary, and this too affects the concentration and fate of these substances in various ways, changing testing results from the same water course over the year, with contamination generally accentuated during low flow conditions. These complexities make for many research studies but few general conclusions.

The basic questions here are about the physical fate of these substances:

· Whether specific pharmaceuticals and other emerging contaminants stick to (are adsorbed by) sediments along the banks and bottoms of streams and rivers;

· What happens to them in groundwater;

· Where and how they concentrate;

· How easily they are degraded by light, biological or chemical interactions, or other processes;

· What chemical products they are changed into;

· Whether they typically survive passage through a drinking water treatment facility; and

· How much is put back on fields in the treated solids from sewage treatment plants or from animal wastes.

As well, as we will discuss in later sections, a crucial question is what adverse effects these low concentrations of chemicals might have.

The short answer to questions about what happens to them in the environment is that it depends on which substance is being scrutinized. Around 150 - 200 of these emerging contaminants have been identified and studied, though the fate of any given substance has not necessarily been researched.

Their behaviour in water is as diverse as their individual chemistry, but there is no question that some are persistent in the environment and some do end up even in treated tap water.

Findings from recent research studies[15] include the following observations:

· After these compounds have been flushed down the drain, or been excreted by people taking drugs, sewage treatment facilities do degrade or remove many of them. However, of the substances largely removed from the wastewater effluent, some, such as the endocrine-disrupting compound nonylphenol, simply partition to the sewage sludge. A percentage of the nonylphenol can be removed from that by aerobic sludge composting, but it is not removed by general sludge digestion processes.[16]

· In a recent study[17] of the Santa Cruz River in Arizona, a stream whose flow is effluent-based, sampling showed different patterns for different sites and substances. For a number of substances, contamination was reduced further downstream compared to samples taken near the outfall from a wastewater treatment plant. However, some drugs – for example, fluoxetine (Prozac) and the antacid cimetidine – did not show up in samples taken in the plant itself but did appear in samples taken downstream. This indicates that some unidentified processes, perhaps desorption, are going on in the stream itself.

· A number of substances are removed from streams and rivers by bank filtration, but some are not. Two compounds that do not get removed and have been suggested as indicators are the drug metabolite of phenazone-type drugs AMDOPH and the anti-epileptic primidone.[18]

· Some compounds are volatilized from water, some react chemically with the water itself, some are sorbed to sediments, some are biodegraded (degraded through biological processes), some are photo-degraded (degraded by exposure to light), and some diffuse into the water body.[19] Some are taken up by plants or animals; according to an article by Sharon

Batt on the Women and Health Protection website, about 30% of pharmaceutical compounds are not soluble in water but are fat soluble, meaning they are likely to enter the food web if they are not degraded. All of these processes may change the concentration in the water or could eventually remove the substance from the water partially or completely. However, as noted earlier, the continuous supply from ongoing use and discarding of these substances means that contaminated water bodies will likely remain so, unless the contamination is caused by an accidental, un-repeated release.

· These different degradation processes may vary with factors like turbidity or pH; the fate of many antibiotics, for example, is profoundly affected by pH.[20] The time required also can vary. For instance, in one study of photo-degradation in water of the beta-blocking drug propanolol hydrochloride in the U.K., seasonally changed conditions allowed a 30% reduction of the drug in less than a day in summer, but only an 8% reduction for the same time span in winter.[21]

· Some pharmaceuticals and other contaminants are persistent, however, even surviving drinking water treatment. For example, in an American survey of more than 100 compounds in a drinking water treatment plant, 22 persisted in treated water; of these, 21 were not regulated. In that study, all samples contained at least 3 - 15 compounds, and some substances, notably DEET, AHTN (musk, used to scent shampoos, etc.), cotinine (the major metabolite of nicotine, excreted by smokers), and carbamazepine (an anticonvulsant), were found consistently in the treated water.[22] Another large study in Minnesota of newly emerging contaminants also identified DEET and carbamazepine as being of particular concern because they are both persistent and mobile (i.e., readily transported in water).[23]

In Canada there has so far been less scientific work done on the fate of emerging contaminants in wastewater or to detect their presence in drinking water. One study, beginning this year and supported through the Canadian Network of Toxicology Centres, is taking place at the University of Guelph. Researchers will create experimental ponds representing different trophic levels (levels of the food chain) in order to study the uptake and fate of a number of widely prescribed drugs.[24]

A widely cited research project about pharmaceuticals in drinking water in Canada was instigated by CTV News in 2003 as part of a journalistic investigation. Drinking water samples from taps in 10 Canadian cities were tested for chemically acidic and chemically neutral drugs and four classes of antibiotics[f] by Enviro-Test Labs, with results confirmed by a second laboratory at Trent University. Pharmaceutical products were found in four samples: carbamazepine in Brooks,

[f] The classes of antibiotics were sulfonmides; quinolones; tetracyclines; and macrolides.

Alberta, Montréal, and Hamilton, and gemfibrozil (a cholesterol drug) in Portage La Prairie, Manitoba. Within the detection limits, no antibiotics were found in the drinking water.[25]

Articles in the *Vancouver Sun* and the *Ottawa Citizen* (by Sarah Staples, November 13, 2004) give results of a more recent study, described as the first government survey of pharmaceuticals in Canadian drinking water, which was undertaken by the National Water Research Institute in Burlington, Ontario for Health Canada and Environment Canada. Researchers tested samples of drinking water from 20 drinking water treatment plants in southern Ontario, concentrating on that local region because that made it easier to preserve the integrity of the samples (not because there were thought to be any special problems there). Tests were done for only a limited range of pharmaceuticals, mainly drugs that are chemically acidic, because these were easier to test for using techniques for pesticide analysis. Eight different drugs and the antimicrobial triclosan were found in the samples, including the painkillers ibuprofen and naproxen, and the cholesterol drug gemfibrozil. Results of the study are expected to be published in a scientific journal.

The early conclusions to be drawn from the scientific work undertaken so far are that some pharmaceuticals and related compounds, notably the insect repellent DEET, the anti-convulsant carbamazepine, and perhaps Prozac, are quite stable in water and should be treated as persistent environmental contaminants. However, other substances that are not as persistent may have significant ecological or human health implications, as we will discuss in the next sections of this report.

4. The Ecological Impacts, Including Human Health Effects, of Emerging Contaminants Detected in Water

There are two major **known** groups of effects related to pharmaceuticals, personal care products, and similar substances that are now being found in water.

· One group is connected to an important subset of pharmaceutical products, namely antibiotics or antimicrobials.[g] As we discuss in detail in Appendix A, the widespread use and presence of these drugs can lead to drug-resistant strains of pathogens, with a resulting rise in the number of diseases and individual infections that don't respond to antibiotic drug therapy. The development of resistance in previously susceptible strains of bacteria is termed *antimicrobial resistance, or AMR*.

· It is important to recognize that the very low concentrations of antibiotics found in surface water or drinking water would probably not be large enough to cause the development of AMR specifically from those drug residues in that water. Resistant bacterial strains most often develop in places where appreciable quantities of antibiotics are regularly used, such as hospitals or in large animal husbandry operations. Concerns regarding AMR in the environment relate mainly to finding these resistant genes or bacteria in soil or water, but the source is likely from fecally contaminated water or agricultural runoff. However, there are unresolved questions about the significance of residues of antibiotics in groundwater and urban wastewater which are being investigated at present, such as in the possible role of sewage treatment plants as reservoirs or incubators for antibiotic-resistant bacteria.

[g] Technically speaking, the term *antibiotics* refers to substances that are biological or natural in origin, while *anti-microbials* is more inclusive, encompassing both natural and synthetic drugs. However, the term *antibiotics* is widely used, even by doctors, to mean both natural and synthetic products, and for simplicity we will use it in this inclusive way.

· The second set of impacts is related to a different group of chemicals whose effects are to disrupt the endocrine systems of living organisms through a variety of mechanisms. These substances, referred to as *endocrine-disrupting compounds or substances (EDCs or EDSs*), include birth control pills, hormones, and various other pharmaceuticals. Other types of products as well incorporate or are themselves EDSs: industrial chemicals such as PCBs, metals and plasticizers; various surfactants, fragrances, and preservatives in cleaning and personal care products; contaminants like dioxins; and pesticides, including the insect repellent DEET. In humans and other large mammals their health effects are not well understood. In fish, birds, and other wildlife, effects have included reproductive impairment or failure, deformities, and feminization.

Other possible effects, for example of sub-therapeutic doses of drugs which are not clearly linked to endocrine disruption, have not been well studied. Some EDS researchers have proposed looking at observable changes in different species in such things as development and behaviour because of uncertainty surrounding the mechanisms through which chemicals can affect living organisms.

4.1 Endocrine-Disrupting Substances (EDSs): Context and Early Warnings

EDSs provide some of the poster child examples of the dangers posed by the new chemicals that were increasingly introduced as part of 20th century life. The discoveries of some of these dangers galvanized many to work toward far-reaching changes in the regulation of pesticides, drugs, and commercial chemicals. But as a cause for concern, the category of EDSs only started to become visible in the 1990s as its mechanisms and effects became better understood.

Writers about the politics of the environment frequently date the present wave of the environmental movement from the 1962 publication of Rachel Carson's *Silent Spring*. The ensuing controversy that swirled around that book was about the wisdom of continuing with the widespread use of pesticides, in particular DDT, and whether these were effectively general biocides rather than just killers of insects. Indeed, Carson herself was quoted as saying that they should be called biocides rather than insecticides,[26] thus orienting discussion of the issues they posed toward questions about lethal toxicity.

However, the impacts on birds that gave the book its title were not just the immediate deaths due to acute pesticide poisoning. They were often reproductive failures also caused by persistent organic pesticides, and occurring, as we now recognize, through the mechanisms of endocrine disruption. But endocrine disruptors were not seen as a large and special class of substances until decades

later. Instead, much of the environmental debate in the 1970s and 80s about the less immediate effects of pollution focused on cancer and the kinds of neurological impairment caused by lead and other heavy metals. The longstanding dread of cancer, for which there had been few effective treatments, was strengthened by the important discovery that there was a delay – the latency period – between the exposure to ionizing radiation or other cancer-causing agent and the development of the disease itself. Partly because of this delay in manifesting itself, as well as its lethality, cancer was implicitly regarded as the most quintessential and significant of possible hidden health effects related to the increasing use of chemicals. Environmentalists pressed for, and eventually got, legislation that required new chemicals and pesticides to be tested for carcinogenicity, a lengthy and complex process, as well as acute toxicity, teratogenicity, and mutagenicity.

In the field of human health, two of the most widely reported stories related to new hazards from chemicals, in this case pharmaceutical products, were the thalidomide and DES tragedies. Thalidomide had been prescribed as a tranquilizer or sleeping pill during pregnancy, but in 1962 – coincidentally, the same year *Silent Spring* came out – the discovery of its connection to babies with dramatic birth defects involving missing or truncated limbs made headlines around the world. And in 1971, the link between the synthetic estrogen diethylstilbestrol (DES) taken during pregnancy to prevent miscarriage and its terrible effects on the female children of those mothers who had taken it was established. These effects were flagged because they were so unusual: clear-cell cancer of the vagina rarely occurred in women under 50, but there were odd clusters of cases in young women, along with other reproductive problems, like deformities of the uterus and reproductive tract. (Later experiments showed that male mice babies were affected as well, but their reproductive defects, such as undescended or stunted testicles, were more common. There is still some debate about whether DES caused problems in human male children.)[27]

Many responded to all these events with a more skeptical and cautious attitude about the positive claims made for new technologies, products, and projects. Such thinking translated politically into attempts to proceed with more forethought, but mainly through more comprehensive and stringent testing and approval processes for new chemicals, drugs, and industrial and other undertakings. Remaining on the margins were initiatives to re-think basic approaches through minimizing risk, or to encourage more holistic scientific understanding through enhanced research and monitoring.

Nevertheless, important things relevant to endocrine disruption and the emerging contaminants issue were learned from these early warnings. Researchers were aware that it was the rare or dramatic nature of the consequences of DDT, thalidomide, and DES that had attracted scientific attention relatively early. They recognized that there might well be more subtle effects of chemicals and drugs that had so far gone unnoticed. It had also become clear that some chemicals could cross both the placental and the blood-brain barriers, once thought to be nearly impregnable defenses against everyday chemical assaults. As well, scientists determined that some effects of

these exposures were delayed, particularly when hormones and similar chemicals were present in early developmental stages: some exposures that happened *in utero* did not show any consequences until that fetus was a young adult. And in the case of chemicals that interfered with fetal development, timing was more critical than dose: some mothers who had children without limbs had taken only a couple of pills of thalidomide during their pregnancies, whereas others who took larger quantities at a different stage had escaped any obvious damage to their babies. It was also noteworthy that some extremely small doses of hormones had devastating impacts.[28]

Two other early research findings were important in directing attention toward endocrine disruption as a cause for environmental concern. Not surprisingly, the first involved the impacts of pollution on wildlife.

· In 1980 there had been a pesticide spill of dicofol into one of Florida's largest lakes, Lake Apopka, which had killed most of its alligators. Years later, wildlife officials looking for sources of eggs for the state's alligator ranching industry couldn't understand why only 18% of the eggs from Lake Apopka renewed population of alligators hatched (normally 90% hatch), or why half of the baby alligators that did hatch died within 10 days. Water sampling indicated the lake was no longer contaminated from the spill; but further research showed that 60% of the male alligators had abnormally small penises. Evidently there were unusual effects on reproduction from minute amounts of some residual contaminant. And this pointed to a connection to reproductive hormones – or something which acted like them.[29]

· Studies in the 1980s of many wildlife species identified a variety of pathologies caused by pollution, such as grotesque tumours in fish in the Great Lakes. Many studies, however, did not turn up elevated cancer rates, but showed various problems specifically related to reproduction, underlining a link to the hormones – the chemical messengers – which directed this system: aberrant mating and parenting behaviour in herring gulls, for instance; turtles of indeterminate gender in Florida lakes; and eggshell thinning in bald eagles and other birds.[30] Studies in Britain detecting estrogens in wastewater treatment plant effluents and finding feminization in fish exposed to such effluent sparked much research focused specifically on environmental estrogens in treated water.

Another line of evidence which suggested substances that acted like hormones should be looked at more closely came from a different quarter: an inexplicable laboratory contamination.

· In 1987, cancer researchers at Tufts Medical School in Boston had been investigating possible mechanisms that would inhibit normal cells from multiplying without restraint, as cancer cells do. For this research, they were using a line of breast cancer cells that

multiplied in the presence of the female hormone estrogen. In order to tightly control results, strict protocols were in place, since any contamination could ruin weeks of experiments. Despite extraordinary care, however, suddenly all the colonies of breast cancer cells the scientists were cultivating, not just the ones treated with estrogen, began to proliferate wildly. Either the cell colonies had been contaminated by estrogen, or by something that acted just like it. It took a frustrating two years of eliminating possibilities and much painstaking analytical work, but the researchers eventually tracked down the problem. They discovered that Corning, the supplier of the laboratory tubes, had recently adjusted the resin mixture used to make the tubes. After many months of work, the research team was able to identify the estrogen-mimicking substance that had leached from the tubes in minute quantities and contaminated the cell colonies: it was p-nonylphenol, one of the alkylphenols family of synthetic chemicals added to polyvinyl chloride (PVCs) and sometimes to polystyrene to make these plastics more stable and resilient. As it happened, many chemicals in that group, alkylphenol polyethoxalates, were used in detergents, pesticides, and personal care products, and would break down into nonylphenols and related chemicals in sewage treatment plants and the environment. Nonylphenol was also used in making nonoxynol-9, used in contraceptive creams. Studies in rats found that in their bodies nonoxynol-9 would break down into nonylphenol. And now it was evident that at least some of this widely used group of compounds could mimic the action of estrogen.[31]

4.2 Focusing on Endocrine Disruption

In July, 1991, scientists from diverse fields working on aspects of endocrine disruption met at an historic scientific conference at the Wingspread Conference Center in Racine, Wisconsin to share experience and insights. They produced a lengthy document, the *Wingspread Consensus Statement*, which laid out their concerns about these substances, identifying what they were certain of, what was predicted by current models, what they judged likely, and what the uncertainties were. They also endorsed a research agenda to improve predictive capability on the issue.

Some of this agenda is now being pursued. And further work since 1991 has led to a somewhat clearer picture, though far more is still uncertain than is definitely known.

The endocrine system directs and controls many of the body's functions, including growth, development, and reproduction. The basic anatomy has been understood for many years:[32]

- The *endocrine system* produces the body's chemical messengers that regulate and coordinate bodily functioning. These chemical messengers are called *hormones*, and they

are produced by the nine *endocrine, or ductless, glands*. They are called "ductless" because they release their products directly into the bloodstream, unlike the exocrine glands, such as the saliva and sweat glands, that channel their products to specific locations in the body. The endocrine glands include the hypothalamus; the pineal gland; the pituitary; the parathyroid gland; the thyroid; the thymus gland; the adrenal glands; the pancreas; and the sex glands, the ovaries and testes.

· Hormones tell the body what to do in several stages: (1) signals from the nervous system, which operates through electrical impulses rather than chemicals, or from the endocrine system itself stimulate hormone production; (2) the hormone molecules are then secreted into the blood**,** where they travel until coming in contact with target cells. (3) *Receptors*, which are large protein molecules on the target cells, are constantly ready to recognize, attract, and chemically bind the hormone molecules to the target cells. (4) Like keys fitting into locks, hormones attach to the receptors, which transmit the message to the interior of the target cells; some hormones, however, like the male sex hormone testosterone, are small enough to penetrate the cell, where they activate specific genes. (5) The target cells then respond to the chemical message. (6) Having delivered the message, the hormone must be turned off so that it doesn't continue to stimulate a response; its molecules are either excreted from the circulatory system by the kidneys, or degraded by enzymes in the blood, liver, kidney, lungs, or the target tissues. Thus, a healthy endocrine system involves accurate and effective signaling of a need for hormones; adequate production of hormones when a need is indicated; their proper reception, binding to targets, and precise transmission of message; and finally their prompt clearance from the body.

· The neurological and endocrine systems together monitor and continuously adjust the levels of hormone production through feedback mechanisms. Mostly this is done through negative feedback, which means that any deficit or excess is simply reversed. For a few hormones, such as those controlling the menstrual cycle, there is a positive feedback mechanism in which the presence of one hormone stimulates production and secretion of another. In virtually all cases, however, the quantities of hormones needed to stimulate a response are almost vanishingly small.

Natural disorders of the endocrine system are usually related to glandular problems like tumours, or over- or under-production of hormones; some 10% of the population in developed countries is affected by such conditions, which include, among other diseases, diabetes and hypothyroidism.[33]

Chemicals capable of disrupting the endocrine system can be either natural, like some estrogens, or synthetic in origin. Such substances work in different ways, some of them complex processes which are not completely understood:

· They can act as *mimics* of a natural hormone, binding to the target cell's receptor in an *agonist response*;

· They can act as *blockers or antagonists,* preventing hormones from delivering their chemical messages; or

· They can affect the production, release, transport, metabolism or elimination of natural hormones.

Curiously, many endocrine-disrupting compounds do not resemble the hormones they mimic in their chemical structure. Some investigators believe that the research focus should be on end results, since the mechanisms by which chemicals in the environment act on cells in subtle ways are not well mapped out. They would focus particularly on functional endpoints in normal reproduction, growth and development, and also behaviour; these may be linked to EDSs, or to some other mechanism, but should be increasingly considered in monitoring and research in ecology and human health.[34] Reflecting this shift in emphasis, some scientists prefer to use the broader term "signal disruption" to describe this category, and the substances implicated in it as *hormonally active agents* or *HAAs.* (Although this terminology has merit, we will continue to use the older phrase EDS in this report, simply because it is still more commonly used.)

Much of the scientific work since the mid-1990s has linked effects on fish and wildlife with exposure to EDSs in water, often water or effluent from sewage treatment. In their website brochure on EDSs, Environment Canada lists as examples impaired reproduction of fish exposed to pulp and paper mill effluent; abnormal reproduction in snails exposed to anti-fouling chemicals applied to ship hulls; depressed thyroid and immune functions in fish-eating birds; and feminization of fish near municipal sewage effluent outfalls, a finding that has been replicated in many studies.

Some of the most dramatic results in fish were reported in 2003 and came from a study done over three years in the Experimental Lakes area of northwestern Ontario. Led by ecotoxicologist Dr. Karen Kidd of the Canadian Department of Fisheries and Oceans (DFO), the estrogen 17-ethynylestradiol was added to the pristine waters of Lake 260. The average estrogen concentration then was 5-6 nanograms per litre, similar to levels found downstream of wastewater treatment plants. Scientists looked at subsequent changes in phyto- and zooplankton, bacteria, insects, and fish before and during the addition of estrogen; in that time span they did not find major changes in the lower levels of the food web, but the fathead minnow population collapsed entirely. When exposed to these levels of estrogen, the male fish produced vitellogenin, an egg yolk protein found only in females. The vitellogenin damaged kidney function in the males, causing many to die. As well, reproduction was impaired in fish of both sexes, with males producing little or no sperm and

females fewer and more immature eggs.[35]

A great deal of the research has looked particularly at sex hormones, natural and synthetic, like estrogens and androgens, and substances which mimic or block them. This is partly because obvious and highly significant effects in animals like feminization and reproductive failure were linked early to these substances, and partly because testing showed so many chemicals had these effects and were turning up in the water. However, more recent research indicates that other glands and products of the endocrine system, such as the thyroid, can also be affected by many of these virtually ubiquitous chemicals.

Some of the most disquieting animal study results have come very recently. A study by a team led by Dr. Michael Skinner at the Center for Reproductive Biology at Washington State University and published in the June 2, 2005 of the prestigious journal *Science* looked at later generations of rats exposed to the known endocrine disruptors vinclozolin, a fungicide often used in vineyards, and methoxychlor, a pesticide used as a replacement for DDT. Pregnant rats were injected with these substances at a period during gestation when the sexual characteristics of the embryos are developing. The male rat pups of those mothers had a 20 percent lower sperm count than normal, sperm that were less motile than normal, and reduced fertility. The startling discovery, however, was that when these male rats were grown and were mated with females that had not been exposed to the chemicals, 90 percent of the resulting male offspring had similar problems, and the effect held for a fourth generation. Such a long term intergenerational effect has never before been documented. It is known that ionizing radiation can affect the fertility of people exposed and also their children's fertility, as well as occasionally causing DNA mutations that can be passed on to future generations. But the effects seen in these rats were not caused by mutations. The researchers identified the ongoing problems as changes in methylation, a process whereby chemical compounds attach to and affect DNA. Skinner believes such changes might play a role in diseases like breast or prostate cancers; he is quoted as saying that this phenomenon will be widespread and that it will be a major factor in understanding how disease develops.[36]

Although such animal studies are very suggestive, the research so far cannot tell us with certainty exactly what the effects of EDSs are on people and other large animals. Proof of a connection to human health effects cannot be as direct and definitive as studies with laboratory animals, since such experiments can't be done on people. This is not uncommon; it took many years before the connection between smoking and lung cancer was widely accepted (and the relationship was ignored or disputed by the tobacco industry for even longer). However, EDS effects will be harder to establish than those of smoking. The quantities of hormones needed to produce natural effects are exquisitely small, and nearly everyone worldwide has some exposure to these many substances. It is not easy to find valid human control groups (like non-smokers in the case of tobacco) for comparisons in epidemiological studies. It is therefore a matter of the slow accumulation of

evidence from animal and clinical studies, along with statistical trends and patterns, that will eventually add up to a widely accepted consensus.

A further confounding factor in researching the effects of estrogens specifically (along with their chemical mimics) in the environment is that they are naturally excreted by humans, other animals, and even produced by some plants (phytoestrogens). The effects of different estrogens and their mimics are not always identical, however. Some of the compounds which mimic estrogen, such as DDT, are not destroyed in the body but remain in fat, and also persist much longer in the environment. They also may have subtly different effects. For example, DES acts as an estrogen mimic in the body, binding to estrogen receptors. Since natural estrogen can disrupt fetal development, the body has developed protective mechanisms during pregnancy: proteins in the mother's and fetus's blood soak up most of the mother's naturally-produced estrogen. But those protective blood proteins do not recognize DES as estrogen, even though the estrogen receptors do, and the fetus of a pregnant woman exposed to DES is thus effectively bathed in higher than normal levels of estrogen.

Other effects are more confusing. In general, natural estrogens, both plant and human, seem to be cleared from the body more quickly than synthetic ones, and when phytoestrogens in food are eaten, they are largely destroyed in the gut. Nevertheless, some studies indicate that plant estrogens can reduce fertility in rats and other animals, and indeed, a number of plants in various herbal medicine traditions are used for their contraceptive powers. On the other hand, some evidence suggests that diets high in plant estrogens from foods like soybeans may have a slightly protective effect against breast and prostate cancers in adults. Since estrogen, both natural and synthetic, has been linked to cancer in many studies, this appears curious. It has been hypothesized, however, that phytoestrogens have a weaker estrogenic effect than natural human estrogen, and so may displace some of the more potent natural estrogens and effectively reduce lifetime exposures.[37]

Some of the suggestive evidence about human health effects of EDSs is related to the incidence of disease and abnormalities that are clearly linked to the endocrine system. Perhaps most noteworthy are the recent rise in incidence of breast, testicular, and prostate cancers, particularly at a time when the overall cancer rates have been declining. All three cancers are linked to the presence of excess hormones. In the United States, breast cancer rates rose 24% between 1973 and 1991; at present, it is the second leading cause of cancer deaths in women after lung cancer, excluding skin cancers (which are the commonest cancers worldwide). In the United States and Canada, one in every seven or eight women will be diagnosed with it. There are a number of risk factors for it, but apart from a genetic predisposition, most of these risk factors are known to be related to increased lifetime exposure to internally produced estrogen. Similarly, testicular and prostate cancer rates have risen; in Ontario, for example, testicular cancer incidence has risen about 60% in the late

1990s, with the fastest increase in the youngest age group. It appears that many of the abnormalities which are associated with it, such as cryptorchidism (undescended testicles), a decrease in testicular size, and hypospadias (abnormalities where the urethra does not extend to the end of the penis) have also increased. In North America, the rate of prostate cancer, which is androgen-dependent, is rising faster than any other cancer in men, though part of this increase is undoubtedly due to improved testing methods, and possibly also to an aging population. A number of cancer specialists are coming to believe that hormone related factors, both from the body and in the external environment, are playing an important role in the increase in these diseases.[38]

5. Responding to Pharmaceutical Products and Other Emerging Contaminants

In Canada, the United States, and many other countries, especially in Europe and Japan, governments, individuals, and other actors have thus far responded to increasing concern about these many substances in several ways.

Basically, there have been three kinds of initiatives:

· Because of compelling evidence and/or public pressure, governments have taken regulatory action on a number of individual substances, particularly endocrine disruptors, but without placing them in the context of a general concern about bioactive pharmaceutical and related compounds in water and the environment;

· Some governments (and we will focus on Canada and the United States particularly) have begun programs to investigate and decide what to do about the hazards and risks of two classes of substances of concern, namely antibiotics and endocrine disruptors;

· Various other actors, including scientific associations, researchers, and academics; industry associations; municipal water treatment managers and individual companies; and granting agencies, environmental and health advocacy groups, and concerned individuals have initiated a variety of actions, which – though uncoordinated – may have many important results.

These three groups of initiatives have included many kinds of specific actions:

· Scientific surveillance, monitoring, and research;

· Regulatory responses;

· Technology evaluation and development;

· Voluntary programs for medical and consumer education and for producer/manufacturer responsibility; and

· Personal choices undertaken by individual consumers, farmers, and companies.

5.1 Societal Response I: Ad Hoc Government Regulatory Actions

Since the 1970s, governments around the world have banned or severely restricted use of many chemicals because of their toxicity, persistence, or bioaccumulation in the environment; many of these, however, are also endocrine disrupting substances, though that was not originally and specifically the reason for their regulation. In Canada, these have included DDT, chlordane, aldrin/dieldrin, mirex and a number of other persistent pesticides and PCBs, the very stable and persistent industrial chemical used in electrical insulators. Dioxins, another group of EDSs, have been largely removed from pulp mill effluent by regulation. The coming into force of two international treaties, the convention on persistent organic pollutants (POPS, which became effective in May, 2004 and essentially banned 12 chemicals) and the Rotterdam Convention for the treaty on Prior Informed Consent (PICS, effective in February, 2004) which curbed exports from industrialized countries of 32 chemicals, will also help to curtail the worldwide use and contamination from some of these dangerous substances.

Some pharmaceutical products are points of contention between countries. The European Union and Canada do not permit recombinant Bovine Growth Hormone (rBGH) to be given to dairy cattle, whereas it is used in the United States. However, this controversy is about genetic engineering and human and animal health, rather than possible residues in the environment.

5.2 Societal Response II: Government Policies and Programs about Antibiotic Resistance and Endocrine Disrupting Substances

Antibiotic Resistance

Antibiotic resistance can be combated at the source, so to speak, by significantly reducing the use of these drugs. Most of the ways to do this involve medical practice. In Iceland, for example, there were excellent drug protocols to avoid creating drug resistance, but despite this vigilance the country had a serious outbreak of penicillin- and then multi-drug resistant *S. pneumoniae* in 1988 (carried in from Spain, as it turned out, by a vacationing travel agent). Iceland restricted even more stringently all use of the resistant drugs, and the incidence of the multi-drug resistant strain dropped to near zero in four years.[39] In this report, however, we will leave most of the discussion and recommendations concerning medical measures such as Iceland's to the health care community, focusing instead on environment-related measures.

The most important other measures involve surveillance, education, and reductions in non-essential antibiotic use in animals. As discussed in Appendix A, antibiotic resistance has been known for many years, but perceptions of it as a high priority problem have varied greatly from one location to another. Countries have also varied in how quickly and drastically they have acted on the problem, in particular the animal use of antibiotics. Sweden, for example, went so far as to ban all animal growth promoters in 1986, even without scientific proof of harm.[40]

By the 1990s, concern was rapidly developing internationally about using antibiotic animal growth promoters and preventive antibiotic additions to animal feed, lest these further increase rising rates of antibiotic resistance in human pathogens. The worry was especially acute about animal use products that came from families of antibiotics that were vital for human medicine, like vancomycin. After Sweden entered the European Union in 1995, that country was granted permission to maintain its ban on growth promoters for four years. After that, it would have to make a scientific case to continue its policy. Meanwhile, Denmark had become fearful about its rising rates of vancomycin-resistant infections, and had banned vancomycin's animal-use relative avoparcin as well as the streptogramin, virginiamycin. The European Union eventually and after much debate extended this ban in all of Europe to all remaining animal growth promoters associated with human medicine, specifically tylosin, bacitracin, and spiramycin.

And in 2003, EU regulations designed to phase out antibiotic animal growth promoters entirely by 2006 were put in place.

In 2001, the World Health Organization (WHO) set up the Global Strategy for Containment of Antimicrobial Resistance. In 2003, that organization endorsed the European phase-out of antibiotics as animal growth promoters.

In the United States and Canada, different governmental health and food and drug agencies have varying views on AMR and animal use of antibiotics as growth promoters. New regulatory initiatives are not pending in either country, although the issue continues to be under intense discussion. The traditional concerns of the regulatory agencies have revolved around drug residues in meat and milk, rather than AMR, and these agencies have not responded very rapidly to the new issues.

In the United States, at least 19 antibiotics are approved by the U.S. Food and Drug Administration (FDA) as animal growth promoters; several of these are closely related to human use antibiotics. However, in 2000, the FDA for the first time attempted to ban the use of a class of human drugs in broiler chickens, in this case fluoroquinolones, as therapeutics specifically because of the potential for increasing drug resistance. One manufacturer, Bayer, took the case to court, where the regulatory decision was upheld, and the ban is now in place. The FDA's approach to the issue is to review the use of drugs as growth promoters on a case by case basis and using a risk assessment methodology. In Canada, the regulatory agency involved, Health Canada's Veterinary Drugs Directorate, is still gathering and assessing information before developing new policies on the issue. One recommendation of Health Canada's *Report of the Advisory Committee on Animal Uses of Antimicrobials and Impact on Resistance and Human Health* in 2002 was to "Evaluate antimicrobials for growth promotion or feed efficiency using sound risk analysis principles and rapidly phase out antimicrobial claims not fulfilling the following criteria: demonstrably effective; involving products rarely if ever used in human therapy; and not likely to impair the efficacy of any other prescribed antimicrobial for human infections through the development of resistant strains." Regrettably, this has not yet been done.

Some of the most significant government actions so far involve setting up systematic monitoring and scientific research programs. The United States put in place an antimicrobial resistance surveillance program, NARMS, in 1996. In Canada, the Public Health Agency leads a multi-agency surveillance program, the Canadian Integrated Program for Antimicrobial Resistance Surveillance (CIPARS) to keep track of trends in antibiotic resistance in humans, cows, swine, and poultry. CIPARS released its second report in March of 2005. Health Canada also provides information and public education of the issue.

The surveillance programs for AMR, however, are linked to health issues; the work on monitoring for antibiotics and endocrine-disrupting pharmaceutical products in water, as described in Sections 3.1 and 3.2, is part of environmental contaminant surveillance programs in both Canada and the

United States. The United States is far ahead of Canada in the extent of its environmental monitoring programs, although Canadian scientists continue to make significant research contributions.

In terms of regulations aimed at keeping antibiotics as well as other pharmaceuticals and toxic materials out of the water, many municipalities have sewer by-laws which prohibit putting various substances into the sewer system; these vary from one municipality to the next. However, such by-law restrictions do not, of course, address the normal process of pharmaceutical elimination in urine and feces, which may be the more important part of the issue. A scattered few municipal water departments, mostly in the United States, have started to do research into the best and most cost-effective wastewater treatment technologies for eliminating pharmaceuticals and other emerging contaminants.

Endocrine-Disrupting Substances

At this stage, the problems with taking action on EDSs start with the fact that there is no scientific consensus even on a list of these substances. There is widespread agreement on some of the most common ones: most persistent organic pesticides (POPs) and similar organic contaminants like PCBs and dioxins; natural and synthetic hormones like estrogen, estradiol, and DES; other pesticides; plasticizers, surfactants and other industrial chemicals such as phthalates, bisphenol A and F, carbon tetrachloride, nonylphenol, and the food antioxidant butylated hydroxyanisole (BHA); and metals such as arsenic, lead, cadmium, and mercury. Several organizations have compiled lists based on published scientific evidence; Environmental Defense's list of suspected endocrine toxicants, as they refer to them, contains over 300 chemicals, and no one thinks that is the definitive number. (By contrast, there are only about 100 commercial antibiotics in use in total.) We include three such lists in our Appendices, taken from the King County website in Seattle, WA; Our Stolen Future website; and Environmental Defense website. Arguably, one of the priorities has to be the development of ways to identify these substances; as yet, there are no internationally recognized screening protocols and tests. As well, there is an extraordinary amount to be learned about EDSs in the environment and their ecological and possible human health effects. Major governmental investments in the related science are needed.

Both the OECD (of which Canada is a member) and the U.S. Environmental Protection Agency (EPA) are developing protocols and screening tests for EDSs; Canada, sensibly, intends to follow their leads in these matters. An internal Canadian policy report on the issue setting out a general direction and key priorities for Canada was developed by the Five Natural Resource Departments Working Group on Endocrine Disrupting Substances, shortened to 5 - NR EDS WG.[41] The report emphasized that much was still unknown, but also made it clear that action was needed. EDSs could be addressed within Canada's existing legislation and regulatory frameworks, it found, but

much more scientific work would be essential. Regulators could use a risk assessment approach, but they must also consider subtle effects and interactions. Canada should not duplicate other national and international work, and should build on its traditional areas of scientific strength, such as field studies. With so many unknowns, the report noted, it was more important to be concerned about functional endpoints in human development, rather than limiting research to particular mechanisms of endocrine disruption. Finally, priorities in research should be the sites, sectors, and populations with the highest potential for adverse effects. These include:

- · municipal effluents
- · intensive agriculture/pesticides/livestock production;
- · textile mill effluent;
- · pulp and paper effluent;
- · mining and metals;
- · historically contaminated sites;
- · already identified areas of concern, such as the Great Lakes Basin; and
- · contaminants in the Arctic.

Key agencies in Canada that are playing leading roles in the issue are Environment Canada, particularly its National Water Research Institute, the Canadian Wildlife Service and the National Wildlife Research Centre, along with various departments and agencies in Health Canada. Environment Canada's Toxic Substances Research Initiative has recognized EDS as one of its priorities.

As well as identifying and doing research on these substances, it is more than likely that governments will need to regulate them. As noted above, some of them are already subject to regulation in Canada, and are even banned, under existing regulatory regimes dealing with pesticides (the Pest Control Products Act), toxic substances (the Canadian Environmental Protection Act - CEPA), and pharmaceutical products and cosmetics (Food and Drugs Act). However, a near-revolution will be required to move away from the current regulatory approach, which is heavily based on proof of specified, clear-cut kinds of harm, such as lethality, birth defects, and cancers. Developing a regulatory policy that focuses on subtle damage and deals with such things as the protection of fetuses from a huge range of substances that affect behaviour, intelligence, and long term reproductive health will be challenging, to say the least. Since regulation is best based on science, there is considerable work to be done to identify the nature of the risks, some of which may be additive or even synergistic. Competing interests and perspectives will, as always, play important roles. So far, Canada has not attempted regulatory action to protect early human development from one common substance for which there is overwhelming evidence of sometimes drastic harm from fetal exposure, namely alcohol.

For new pharmaceutical products in particular, since 1999 the European Medicines Agency

(EMEA) has been working on various drafts of a guidance document on environmental risk to accompany applications to market new active pharmaceutical substances, applying as well to their metabolites and possibly *excipients* (the substance, like a capsule coating, in which the drugs are delivered). Canadian scientists have also been involved in the development of this document, and Canada may eventually incorporate a similar approach. The recent drafts of this guidance reflect developing concerns about pharmaceuticals as emerging contaminants, and for the first time a pharmaceutical regulatory approach will generate much-needed chronic ecotoxicity data from the outset of testing. (The U.S. Food and Drug Administration [FDA] also requires chronic ecotoxicity data, but later in the assessment.) The document provides a two-tiered approach. In pre-screening there is a rough calculation of the drug's predicted environmental concentration (PEC), which eliminates substances whose concentrations are deemed too low to be of concern. However, the guidance does state that endocrine disruptors and other drugs likely to have effects at very low concentrations may need to be addressed regardless of quantities in the environment. The EMEA's trigger for an environmental risk assessment is a PEC of 0.01 micrograms per litre of surface water; the trigger for the FDA is calculated differently, but the comparable PEC is larger by a factor of 10, that is, 0.1 micrograms per litre of surface water. In the draft EMEA guidance document, soon expected to be finalized, Tier A testing includes studies on the drug's aquatic fate and effects (degradability, potential for bioaccumulation, adsorption on sewage sludge, and toxicity to sewage microbes), along with long-term effects tests on fish, water fleas, and algae. These results are used to assess the predicted "no effect" concentration (PNEC) on these species, and, along with the drug company's projected sales, provide an overall PNEC. If these results give a PEC that is lower than the PNEC, the risk assessment is concluded. If it is higher, there is additional Tier B testing to further investigate risk to the environment, including possibly the drug's metabolites.[42] This type of PEC/PNEC risk assessment is becoming a standard way of approaching environmental risk for many emerging contaminants and prioritizing possible regulatory action.

Other levels of government play regulatory roles, as well. As discussed above, municipal sewage by-laws may be useful to prevent some EDSs such as birth control pills from being discarded down drains and toilets. Similarly, a number of municipalities like Toronto have by-laws restricting both public and private applications of pesticides and herbicides in their boundaries.

Provinces also have permitting or licensing roles for pesticide use, industrial emissions, and solid and hazardous waste, as well as drinking water quality and protection. All of these powers, however, are best suited to regulating easily specified actions, products, or chemicals. With EDSs, it is probably still too early to consider specific provincial regulation, except where these chemicals already clearly fit into existing health and environment legislation, such as permits for pesticide use or industrial discharges. However, important areas for both provincial and municipal investigation related to both AMR and EDSs are livestock operations, especially waste disposal, and municipal

sewage treatment and sludge disposal. In these areas, some water treatment technologies may prove to be superior at removing these substances, both from drinking water and wastewater, and this is likely also true for animal waste and sewage sludge practice. Investigation into these technologies and practices should be a priority.

There are also non-regulatory roles that all levels of government can play in public education and in promoting safer or more environmentally friendly alternatives. These include product standards, environmental and other consumer information programs, the promotion of voluntary stewardship programs, labeling, and procurement policies. However, for these as well as all other actions, the biggest problem is the lack of good information on the problem's scale or even presence.

5.3 Societal Responses III: Civil Society and Personal Initiatives

There are a large number of actors in civil society. Some of their efforts discussed here are highly focused on antibiotics, others on EDSs, some on both, and some on broader issues even than the huge and growing category of emerging contaminants. Consequently, we have organized this section by reviewing four kinds of action approaches that apply to **all pharmaceutical and other products** implicated in endocrine disruption, in particular **pesticides, plastics, cleaning agents and personal care products.** These four approaches are (1) *reducing use* of these drugs and other products; (2) finding ways of *making essential use more ecologically responsible*; (3) *making disposal safer*; and (4) *public awareness and advocacy*.

Reducing Use

Reducing use, of course, does not mean that people should do without medication, household cleaners, or shampoo. Our focus will be on consumer alternatives. Particularly in the context of AMR, doctors, public health officials, and other medical experts have made many recommendations about reducing and better targeting of antibiotic use and paying greater attention to hygiene, especially in a hospital setting. However, we will leave discussion and recommendations primarily for medical professionals to be made by the medical profession.

· ***Supporting organic methods in livestock production, farming, and home gardening***
Individual farmers, consumers, and gardeners have supported organic production for decades, thus avoiding hormone implants in cattle, antibiotics used as growth promoters and to prevent disease in large commercial livestock operations, as well as avoiding pesticide use. In the last few years, several large companies have also moved in this direction. Loblaw's, a retail grocery chain, now

carries an extensive line of organic food items, including produce and white and whole grain flour; in 2003 the fast food chain McDonald's, the largest purchaser of beef in the United States and among the largest for chicken and pork, directed its own suppliers to avoid antibiotic growth promoters and will consider it a favourable factor in choosing its independent suppliers; and the coffee shop chain Starbucks carries organic coffee and promotes organic approaches in its suppliers. As well, the Liquor Control Board of Ontario (the LCBO) has begun to offer a limited selection of organic wines.

· *Using alternative and organic cleaners and personal care products like soaps, shampoos, deodorants*

Standard commercial types of these products are mainly of concern because they contain EDSs, and some cleaners have antibacterial agents (ordinary soap and water will adequately control germs). It is difficult to be certain about all the ingredients of many "alternative" products, but some companies that make personal care products, such as Aubrey Organics and the Canadian companies Druide, in Pointe Claire, Québec, and the Green Beaver Company in Hawkesbury, Ontario, are very conscientiously trying to avoid using environmentally questionable ingredients such as phthalates (widely identified as an EDS) and parabens.

Ecologically Responsible Use

Making essential use more ecologically responsible primarily means increasing knowledge about pharmaceuticals, other emerging contaminants, and their effects, especially EDSs. It also means finding or developing technologies to better remove these substances from drinking and waste water.

· ***Scientific knowledge***

This is the most basic and critically important part of the issue right now. There are a growing number of research projects in universities across Canada, and granting agencies are also becoming more interested in projects in this area. Even high school students can sometimes contribute: as a science project in 1999, West Virginia high school student Ashley Mulroy decided to test water in the Ohio River for three antibiotics, penicillin, tetracycline, and vancomycin. She found the drugs in all samples. She then went on to test local tap water for the same substances, and to her surprise these pharmaceuticals were present in the drinking water samples as well. Her work won the prestigious Stockholm Junior Water Prize and was a wake-up call to many scientists.[43]

· ***Evaluating and designing better water and sludge treatment technologies***
In terms of removing pharmaceuticals and other EDSs, research to date clearly indicates that not all technologies and practices are equally effective – or perhaps ineffective. There is considerable scope for private companies as well as municipal water utilities to investigate and develop improved facilities and practices, and a few are already doing so. As well, research is being done and more is needed on wastewater treatment and AMR.

Safer Disposal

Making disposal safer may require better technology to ultimately dispose of discarded pharmaceuticals and other EDSs. It also means public education programs, household hazardous waste programs, and product responsibility (take-back) programs for unused drugs.

· ***Disposal technology***
It is not clear what the best means of disposing of unused pharmaceuticals and EDSs might be. Neither wastewater nor landfills are suitable. Old hospital incinerators were designed mainly to get rid of biologically contaminated waste; many are now shut down because of environmental problems, and would certainly not be a good disposal alternative. Very complete incineration at extremely high temperatures is a possible option, but there are many objections to this technology, based on poor or unreliable past performance. As with water treatment, there are opportunities for private companies to find better solutions.

· ***Public education and product stewardship programs***
Many pharmacies will take prescription and other drugs back for disposal. In British Columbia, a provincial voluntary product stewardship program by pharmacies for returning unused medications that was set up in 1996 reports that some 90% of the province's pharmacies participate. Some pharmaceutical companies have public education programs about proper use and disposal of their products.

Public awareness and advocacy

Many non-governmental environmental and health organizations have become involved in providing information to the public about these issues. A much smaller number are leaders in developing, analyzing, and promoting public policies and programs related to pharmaceuticals and other emerging contaminants detected in water, or on AMR and EDSs in particular. Notable advocacy groups include the Union of Concerned Scientists in the United States on AMR and Environmental Defense on EDSs.

Theo Colborne, a senior scientist with the World Wildlife Fund and her colleagues maintain a very up-to-date and informative website, Our Stolen Future, on EDSs.

6. Conclusion and Recommendations

Although this report's purpose is to provide background and other information on the issues related to emerging contaminants, especially pharmaceuticals, personal care products, and endocrine disruptors now being detected in water, the values driving this initiative are about environmental quality, ecological integrity, and human health and well-being. Some of the societal responses recommended here are not focused only on contaminants in water but address the environment and human health more generally. And yet, pro-actively embracing and acting on broader environmental and health goals may be one of the most effective ways to approach the narrower issue of emerging contaminants like pharmaceuticals in water.

The following are recommendations for action at this time. Despite the early stage of the issues, many people want to know what they, as well as society in general, should be doing. These recommendations are intended to provide a range of useful actions; they are not particularly targeted at governments or specific other actors. It also should be understood that these actions taken together are not the same thing as a strategy to address these issues. A true strategy requires that we know enough about the issues to be able to prioritize the problems and weight our efforts accordingly. By contrast, these recommended actions could and should involve many different activities, programs, organizations, and individuals from various sectors of society. They are primarily aimed at reducing environmental contamination, and only secondarily at immediate, personal consumer protection. In other words, though consumers will certainly wish to reduce their own toxic exposures, and actions like these will help to do that, the recommendations are mainly about all actors' ecological responsibilities for their behaviour, including individuals as well as all levels of government and corporations. Thus, some of these recommendations only make minor direct contributions toward getting pharmaceuticals and other contaminants out of the water, but they are important for moving toward a culture of environmental stewardship.

Although we don't attempt to rank these recommendations in terms of their priority, it must be emphasized that at this time, the single most important task – and one vital to most other actions –

is to define the scale and significance of the problems, using the best science available.

1. Consult and develop a process to determine priority endocrine disruptors in sewage and industrial effluents and review licensing of pharmaceuticals and other chemicals as well as effluent permits in that context.

2. Significantly increase research efforts and funding for science related to these issues, including surveillance and monitoring, environmental risks, ecological science, and human and wildlife health.

3. Increase research on municipal water treatment technologies that better remove pharmaceuticals and related compounds, and provide ongoing information on such technologies for municipalities. Develop related information programs as part of municipal infrastructure support programs.

4. Phase out use of antibiotics and of hormones as animal growth promoters and review the use of preventive antibiotics in animal feed for eventual phase out. Immediately prohibit human use classes of antibiotics for growth promotion and routine prophylactic uses in poultry and livestock operations.

5. Review sewage sludge and animal manure management practices in light of issues related to pharmaceuticals and resistant bacteria in water.

6. Support (and/or practice) organic agricultural production; in particular, organic or at least "natural" meat, fish, and dairy products (or eat vegetarian alternatives).

7. For personal care and cleaning products, as an interim measure increase public education now through an environmental labeling program and/or identification of products free of both suspected endocrine disruptors and antimicrobial substances linked to antibiotic resistance. As more information

is acquired, ban problematic ingredients.

8. Support or develop province-wide product stewardship programs for return of unused drugs.

9. Support or develop municipal by-laws banning pharmaceuticals and other chemical discards in sewers and restricting pesticide use; ensure enforcement capability and action.

10. Increase support for public education and awareness programs on these issues and leadership to develop action initiatives.

11. Identify stakeholders and initiate public discussion and multi-stakeholder consultation in prioritizing government actions, problem areas, and what to do about both.

End Notes

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10. "Environmental Fate and Effects of Chemicals Associated with Canadian Freshwater Aquaculture" by Robert J. Scott, Department of Biology, University of Western Ontario [no date listed]. Available at Fisheries and Oceans website, www.dfo-mpo.gc.ca/science/environmental-environnement/sok_enviroeffects_aquaculture/exec_scott_e.html+hor

11. Women and Health website, available at www.whp-apsf.ca/en/documents/pharmWater.htl

12. "Survey of the New York City Watershed for the Presence of Pharmaceuticals," by Wilson, Lloyd, New York State Department of Health; Patrick O'Keefe, Wadsworth Center for Laboratories and Research; Patrick Palmer, New York State Department of Health; Robert Sheridan, Robert Briggs, and Thomas King, Wadsworth Center for Laboratories and Research. Presented at the 4th International Conference on Pharmaceuticals and Endocrine Disrupting Chemicals in Water, October 13-15, 2004, Minneapolis, Minnesota

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States Geological Survey website at toxics.usgs.gov/regional/emc/

14. Reports of this study are available at a number of websites, such as CTV's website at www.**ctv**.ca/servlet/ArticleNews?study/CTVNews/1035152496332_232?s_name=&no_ads=

15. These were all reported in papers given at the National Groundwater Association's 4th International Conference on Pharmaceuticals and Endocrine Disrupting Chemicals in Water, held in Minneapolis, Minnesota October 13-15, 2004, available in the Proceedings

16. "The Fate of Nonylphenol and Total Estrogenic Activity During Wastewater Treatment and Sludge Digestion: A Mass Balance Analysis" by David M. Quanrud, Jianmin Zhang, Sondra Teske, Hao Dong, P. Orosz-Coghlan, Pete Littlehat, Otakuye Conroy, Robert G. Arnold, Wendell P. Ela, and Kevin E. Lansey, University of Arizona (reference End Note 15)

17. "Temporal Occurrence and Persistence of Pharmaceuticals, Pathogens, and Other Wastewater Compounds in an Effluent-Dependent Stream, Tucson, Arizona" by Gail Cordy, U.S. Geological Survey; Normal Duran, U.S. EPA; David Anning, Ed Furlong, Steve Zaugg, and Dana Kolpin, U.S. Geological Survey (reference End Note 15)

18. "Transport and Attenuation of Pharmaceuticals and Pesticide Residues During Bank Filtration and Their Relevance for Drinking Water Supply in Berlin, Germany" by Thomas Heberer, Federal Institute of Risk Assessment, Berlin (reference End Note 15)

19. "Pharmaceuticals and Other Organic Wastewater Contaminants in Water Resources of the United States: Research by the U.S. Geoplogical Survey's Toxics Substances Hydrology Program" by Dana W. Kolpin, Edward T. Furlong, Michael J. Focazio, Michael T. Meyer, Steven D. Zaugg, Larry B. Barber, and Kimberlee K. Barnes (reference End Note 15)

20. "Determination of Acid Dissociation Constants (pKa) for Veterinary Antibiotics by Potentiometric Titration" by A. Qiang and C. Adams, University of Missouri - Rolla (reference End Note 15)

21. "Roles of Partitioning and Phototransformation in Predicting the Fate and Movement of Pharmaceuticals in U.K. and U.S. Rivers" by Qin-Tao Liu, Andrew M. Riddle, Paul F. Robinson, and Neil Gray, AstraZeneca Global Safety Health and Environment (reference End Note 15)

22. "Fate of Organic Wastewater-Related Contaminants in a Drinking Water Treatment Plant" by Paul Stackelberg, Edward Furlong, Steven Zaugg, Michael Meyer, and Jacob Gibs, U.S. Geological Survey; R. Lee Lippincott, New Jersey Department of Environmental Protection (reference End Note 15)

23. "Pharmaceuticals and Other Wastewater Contaminants in Waste, Surface, Ground, and Drinking Waters of Minnesota" by Kathy E. Lee, Dana W. Kolpin, Edward T. Furlong, and

Michael T. Meyer, U.S. Geological Survey (reference End Note 15)

24. Information about this study is available at www.uoguelph.ca/atguelph/02-05-08/articles/drugs.html

25. This report is available through links at the CTV News website, found at www.**ctv**.ca/servlet/ArticleNews/story/CTVNews/1044053088271_39462288/?hub=SciTech

26. Carson is quoted as saying this in her obituary in the *New York Times*, found at www.nytimes.com/books/97/10/05/reviews/carson-obit.html

27. Colborn, Theo, Dianne Dumanoski, and John Peterson Myers. *Our Stolen Future*. New York, London, Victoria, Toronto, Aukland: Dutton, a Division of the Penguin Group, 1996. This account, as well as much other information, is found in Chapter 4, "Hormone Havoc"

28. Page 50, *Our Stolen Future*, referenced in End Note 40

29. Page 6, *Our Stolen Future*, referenced in End Note 40

30. See Chapter 2, "Hand-Me-Down Poisons" in *Our Stolen Future*, referenced in End Note 40

31. This account is abstracted from the much longer, and very interesting, story of scientific detective work in Chapter 8, "Here, There, and Everywhere" in *Our Stolen Future*, referenced in End Note 40

32. Information on the endocrine system is available from many sources; the descriptions used here are based on material in the volume *The Endocrine System* by Marjorie Little, 1990, in the Chelsea House Publishers series, *The Encyclopedia of Health* (New York, Philadelphia)

33. Page 24, *The Endocrine System*, referenced in End Note 45

34. Website of the National Water Research Institute, available at www.nwri.ca/threatsfull/ch5-2-p.html

35. This account is based on an article in the August 7, 2003 Science News section of *Environmental Science & Technology Online*

36. Quoted in a June 3, 2005 article, "Effects of some toxins inherited, study finds," in the *Toronto Star*

37. Natural and synthetic hormones are discussed at length in Chapter 5, "Fifty Ways to Lose Your Fertility" in *Our Stolen Future,* referenced in End Note 40

38. For example, an editorial titled "Why Is the Rate of Testicular Cancer Increasing?" in the

Canadian Medical Association Journal in January 26, 1999 by University of Toronto doctor Laurence H. Klotz emphasized the possible role of environmental pollutants with estrogenic or antiandrogenic activity

39. Pages 182-183 in *The Killers Within*, referenced in End Note 6

40. Page 137, *The Killers Within*, referenced in End Note 6

41. This report, *Endocrine Disrupting Substances*, is by Mark Servos, Peter Delorme, Glen Fox, Roger Sutcliffe, and Michael Wade, and is available at the National Water Research Institute website at www.nwri.ca/threatsfull/ch5-1-e.html

42. Most of this information appeared in *Environmental Health Perspectives*, Volume 113, Number 10, October 2005

43. This story is recounted at a number of websites, such as www.purewatergazette.net/antibiotics.htm

Glossary and Acronyms

Adsorption: The adhesion of a thin layer of molecules to other kinds of substances with which they are in contact

Agonist response: Response by a target cell to a chemical which mimics the action of a natural hormone and binds to the target cell's receptors

Antagonist response: Response by a target cell to a chemical which blocks natural hormones from binding to the target cell and delivering their message

AHTN: A synthetic musk compound

AMDOPH: A metabolite of phenazone-type drugs used as analgesics

AMR: Anti-microbial resistance; the development in previously susceptible bacteria of resistance to anti-microbial drugs

Androgens: Male sex hormones

Anthropogenic: Created or caused by human activity

Antibiotics and anti-microbials: Substances which kill bacteria or prevent them from reproducing; antibiotics are biological or natural in origin, while the term anti-microbials is more inclusive, applying both to natural and synthetic drugs. However, the term antibiotics is widely used to refer to both natural and synthetic products in everyday language

BHA: The food anti-oxidant butylated hydroxianisole, a suspected endocrine disruptor

CEPA: The Canadian Environmental Protection Act

CIPARS: The Canadian Integrated Program for Antimicrobial Resistance Surveillance, led by the Public Health Agency and intended to keep track of trends in AMR in humans, cows, swine, and poultry

DEET: An acronym for the abbreviated name of an insect repellent chemical, diethyl toluamide

DES: An acronym for the synthetic estrogen diethylstilbestrol, once prescribed to prevent miscarriage

EDCs or EDSs: Endocrine-disrupting compounds or substances

EMEA: The European Medicines Agency

Endocrine system: The system that controls many of the body's functions through hormones,

chemicals produced by the body's nine endocrine, or ductless, glands and carried in the bloodstream to many sites in the body, where they bind chemically to receptors on target cells

EPA: The U.S. Environmental Protection Agency

Estrogens: Female sex hormones

Excipients: Substances, like a capsule coating, in which drugs are delivered

Extra-label or off-label use: The unlicensed use of human drugs to treat other animals; in most jurisdictions, this practice is legal if the drugs are prescribed by a veterinarian

FDA: The U.S. Food and Drug Administration

Hormones: The body's chemical messengers, which regulate and coordinate many functions, including growth, development, and reproduction

HAAs: Hormonally active agents, a term some scientists prefer to use to describe chemicals that act to disrupt the various mechanisms for signaling and control in the body, including endocrine disruption but not limited to that mechanism

Methylation: A process whereby chemical compounds attach to and affect DNA

NARMS: An AMR surveillance program put in place by the United States in 1996

PEC/PNEC: The predicted environmental concentration/predicted "no effects" concentration; a ratio used to review environmental risk for a substance

Photo-degrade: Degrade through exposure to light

Phytoestrogens: Natural female hormones produced in plants

PICS: Refers to the Rotterdam Convention on Prior Informed Consent, effective in February 2004, concerning the export of chemicals from industrialized countries

POPS: Refers to the international convention on persistent organic pollutants, which came into force in May, 2004

PPCPs: Pharmaceuticals and personal care products; one grouping of emerging contaminants that are excreted and/or discarded into or washed away with wastewater and that are now regularly detected in water

rBGH: Recombinant bovine growth hormone

Signal disruption: A term some scientists now prefer to use instead of endocrine disruption to describe the various chemical mechanisms that can subtly disrupt the body's ability to send the signals that control and direct functioning and development

Sorb: To take up and hold through adsorption or absorption

Appendix A: Drug Resistant Bacteria

It is generally thought that drug resistance in bacteria, or AMR, probably does not develop in surface water in the environment as a result of the low concentrations of antibiotics that are now being detected in that water. This is because the dilution effect is so great; those drug levels are not large enough to be toxic to microbes and therefore to promote the selection of resistant bacteria. The venues where AMR is most likely to develop are in hospitals or in connection with intensive animal farming operations and their waste disposal practices. However, whether there are any specific effects on the selection, promotion, and maintenance of resistance from the discarding and excretion of drugs into wastewater remains at this time unknown. Further research is continuing into such questions as whether sewage treatment plants themselves have any role in AMR, though without any broad conclusions as yet.

Nevertheless, AMR is certainly a result of the extensive use (and misuse) of antibiotics discussed in Sections 2, 2.1, and 2.2 of this report. Therefore, for the benefit of readers interested in pursuing information and issues related to the overuse of antibiotics and antibiotic resistance, this Appendix provides additional background on the science and costs of AMR, which is becoming a very serious problem worldwide.

The Development of Drug Resistant Bacteria

The appearance of AMR is not a new or unanticipated problem.

The first commercial antibiotic, penicillin, came onto the market in 1943, and it truly was a wonder drug, treating many infections and dramatically improving survival rates in surgery and serious wounds. But by 1945, penicillin's discoverer Alexander Fleming was publicly cautioning that its indiscriminate use would lead to the development of resistance in the large class of bacteria that penicillin can treat, so-called Gram-positive bacteria.[44] Despite this warning, however, penicillin continued to be widely prescribed and also at that time used in many over-the-counter products such as throat lozenges and soaps. And not surprisingly, penicillin-resistant strains of one of the commonest infection agents, *Staphylococcus aureus,* did begin to appear, the resistant strain rapidly rising to 14% of *S. aureus* infections in American hospitals by 1946, and increasing to 59% by 1948.

The discovery of penicillin was more accident than predicted by theory. The mechanisms of how the antibiotic actually worked, as well as how bacteria might become resistant to it and other drugs, took decades to understand.

Bacteria are microscopic in size, usually just one cell, and have one defining characteristic: they lack a cell nucleus surrounding their genetic material. They are among the most numerous and are also probably the oldest of our planet's life forms. For hundreds of millions of years they multiplied in water and, later, in soil, using one another as food and continually evolving ever more sophisticated methods of chemical attack and defense.

Gram-Positive and Gram-Negative Bacteria

In 1884, a Danish doctor, Hans Christian Gram, noted that some bacteria retained a particular staining dye, while others did not. It turned out that those that did – "Gram-positives" – have an enclosing single-layer cell wall, and those that did not, "Gram-negatives," don't have a cell wall on the outside but instead have a two-layer cell membrane. This different reaction to staining dyes proved to be useful as the basis for categorizing bacteria into these two types, since there are a number of traits associated with one group or the other. Especially important is the differing susceptibility of Gram-positive and Gram-negative bacteria to various classes of antibiotics.

The penicillin family of antibiotics are the chemical products of molds, a kind of fungus; other families of antibiotics come from bacteria with natural chemical defenses against certain other bacteria. (Synthetic antibiotics, or, technically, anti-microbials, are novel compounds created by chemical manufacturing processes rather than biological ones; however, many modern antibiotics involve chemical modification of the basic natural-source molecules.)

Many species of bacteria eventually evolved to live in or on animals, including humans, using them as a source of food or a convenient living environment, some species even providing services like helping to digest the host's food. (Bacteria living harmlessly in or on a host are termed *commensals.*) Disease-producing bacteria cause infections by invading a wound or overrunning some part of a human's or other animal's body, using it as a source of nutrients but in the process creating mayhem in the host's cells. Antibiotics work either by chemically interfering with the disease bacteria's ability to reproduce (these drugs are called *bacteriostatic*), or by actually killing the bacteria (these are called *bactericidal*). Specific mechanisms include causing the disease bacteria to *lyse* or disintegrate by inhibiting maintenance of its cell wall, or interfering with the bacteria's metabolic processes or its synthesis of protein, DNA, or RNA. After antibiotics initially knock back many of the invading bacteria, the immune system of the host – that is, of the patient – takes up the fight and overwhelms the remaining infection-causing bacteria.

Strains of bacteria that become resistant to antibiotics can develop in several ways.[45]

Some individual bacteria may be generally tougher, or through a chance mutation have a degree of *natural immunity* to the drug. As noted earlier, bacteria and fungi have been competing – metaphorically waging chemical warfare – for much of the Earth's history, and have evolved many

mechanisms to withstand attack or out-compete other micro-organisms. At the molecular level, resistant bacteria may be able to prevent the antibiotic from being taken inside their cell walls or membranes. Or bacteria may be able to block the drug from binding to its target within the cell, or even be capable of producing chemicals that destroy the antibiotic.

If some stronger or naturally resistant bacteria survive an encounter with an antibiotic, that strain will have an evolutionary advantage in the presence of the drug. With repeated exposure the strain will tend to be dominant. This can happen if a patient stops taking a drug before the end of the full course of the treatment and the surviving bacteria multiply, sometimes producing a resurgence of the infection. It can also occur if antibiotics are introduced into the wider environment at concentrations that are toxic to the bacteria. Because bacteria produce new generations so quickly, they can develop resistant strains much faster than evolutionary change happens in larger animals. Under good conditions, some bacteria can reproduce asexually by dividing, and thus doubling their numbers, every 20 minutes.

As well, bacteria can acquire their immunity directly from the genetic material of other bacteria that have become resistant. This is not just a matter of passing along the resistance genes from one generation to the next, as in ordinary reproduction. Not only is natural mutation a normal and continuous process in bacteria, but these organisms can get resistance genes directly from each other, including from bacteria of other species. Direct transfer of genetic material among bacteria can occur in several ways:

- Some bacteria can *conjugate*, that is, get together to exchange genetic material through a cell bridge, thus providing greater variability and resilience than cell division allows;

- Some bacteria can scavenge and then incorporate DNA remnants into their own genetic material from dead bacteria in a process called *transformation*;

- Bacteriophages, sometimes just referred to as *phages*, are viruses that infect bacteria, and can carry genetic material between bacteria in a process called *transduction*.

Genes for antibiotic resistance can be carried and transferred separately from the bacteria's regular "package" of chromosomes. Small, circular pieces of DNA called *plasmids* containing 5-100 genes can exist and replicate in a cell independently of the chromosomes. They code for a few proteins that are not coded for by the chromosomes packed together in the cell's interior (the nucleoid). Plasmids are not necessary for normal cell growth. It seems they essentially provide additional options that may, under certain conditions, become extremely useful – such as carrying genetic instructions for antibiotic resistance. And *transposons,* even smaller mobile segments of DNA which are also capable of independent replication, code for an enzyme that allows them to randomly insert copies of themselves into a new position within the same or another chromosome or plasmid, thus changing the bacteria's genetic instructions. They, too, can carry antibiotic resistance genes.

With these various mechanisms at their disposal, the ability of bacteria to adapt to antibiotics is truly formidable. For the last 60 years, researchers have been able to add new drugs to the arsenal of effective antibiotics even as resistance developed to older pharmaceutical products. But a strategy of trying to outpace the development of antibiotic resistance by the creation of new antibiotics cannot ultimately be a winning one. Not only do bacteria evolve too quickly, but powerful new antibiotics may induce the development of more virulent strains of pathogens. By borrowing genes from distant relatives, some bugs have become resistant to synthetic drugs for which no previous natural immunity could have existed. Humans have effectively, though inadvertently, developed these pathogens.

There is really only one way for people to outmaneuver AMR: by tackling the evolutionary pressures that create resistance. This requires significantly reducing the quantity of antibiotics in use. There are both direct and indirect ways to go about this. Indirectly, there are changes in medical practice that could reduce the need for antibiotics, such as better control of the spread of serious infections in the first place (e.g., through better hygiene, both in and outside hospitals) and the development of better targeted or alternative therapies and preventive approaches (e.g., phage therapy or new vaccines). But, as we emphasize in this ecologically-focused report, it is also possible to phase out altogether some current non-therapeutic uses of antibiotics.

Antibiotic Resistance and Human Health Effects

Bacteria are everywhere. The commonest pathogenic ones are sometimes variant strains of general types that normally harmlessly inhabit human and other animals' gastrointestinal systems, throats, noses and skin. When they multiply rampantly or invade elsewhere in the body, which can happen in patients with wounds or undergoing surgery, or with an immature immune system or one weakened by chemotherapy or even just a bout of influenza, these bacteria can cause very serious illness. Common infectious agents include:

- Enterococci that are ordinarily harmless and are found in the digestive tract, but that can in hospitalized patients invade the skin and bloodstream and sometimes cause heart valve and other infections;

- Streptococci, normally living in the throat, that are the source of sore throats, earaches, and also bronchitis, pneumonia, bacterial meningitis, and the flesh-eating disease, necrotizing fasciitis; and

- Staphylococci, found in the nose or on the skin in a substantial number of the healthy human population. One of the most virulent types is *S. aureus*, which, once in the bloodstream, is capable of causing surgical infections, pneumonia, heart and brain infections, and fatal systemic infections involving toxic shock.

The so-called Big Three, which produce many of the commonest infections, are *Enterococcus*

faecium, causing a wide range of infections when it establishes itself outside its natural home in the gut; *Staphylococcus aureus*, when introduced into the bloodstream able to cause many very serious infections; and *Streptococcus pneumoniae,* the cause of respiratory infections and pneumonia as well as some 6 million earaches a year in American children. According to the Centers for Disease Control (CDC),[46] each year in the United States *S. pneumoniae* causes up to 135,000 hospitalizations, *E. faecium* makes 15,000 people ill, and *S. aureus* affects, with varying severity, as many as 9 million people. The latter two bugs primarily cause infections in hospitals, but *S. pneumoniae* occurs in the community as well as in hospitals.

Antibiotics

Various chemicals can kill bacteria outright, but usually harm other living cells, too. What sets antibiotics apart is their ability to interfere with specific life-supporting mechanisms in disease-causing bacteria cells, but without killing the patient – though some antibiotics are quite toxic and individuals can have dangerous allergic reactions to particular drugs. Antibiotics have no effect on viruses, such as those that cause SARS, colds, and flu.

Many food-borne illnesses that result in vomiting or diarrhea are also caused by bacteria. Some newly-emergent strains are more virulent than in the past. These include *E. coli* 0157:H7, emerging as a threat in the 1980s and responsible for the Walkerton, Ontario deaths; *Campylobacter,* carried chiefly by poultry, now causing 2 million infections and between 50-100 deaths a year in the United States, with one in every thousand cases resulting in the paralyzing Guillain-Barré Syndrome; and *Salmonella*, which causes 1.4 million cases and between 500-600 American deaths a year. The DT104 strain of *Salmonella*, which is particularly deadly, is now resistant to 5 antibiotics, and resistance has increased from less than 1% in 1980 to 34% by 1996. In the United States, these latter two bacteria account for 80% of food-borne illness and 75% of related deaths, many due to multi-drug resistant infections.[47]

Globally, one of the most worrisome developments in bacterial drug resistance has been the return of tuberculosis. These bacteria, *Mycobacterium tuberculosis* and its close relatives, have increased their spread of illness dramatically due to the global rise of HIV infection as well as worsening economic conditions in the former Soviet Union and poor living conditions in the developing world. The World Health Organization (WHO) reports up to 50 million people world wide with multi-drug resistant tuberculosis (MDR TB), almost all of those cases outside North America.[48]

By the mid-1950s, it had become apparent that resistance not just to penicillin but to a number of related antibiotics was growing and some patients were dying because of it. Half of all *S. aureus* infections in hospitals by then were not responding to most available antibiotics.[49] However, pharmaceutical companies developed new drugs, and serious concern in the medical community about drug resistance only began to be widespread in the 1990s. Not only had the pace then slowed for the successful research and marketing of new antibiotics, but the new drugs tended to

be more toxic or difficult to administer, and also much more expensive. The situation began to be felt as a crisis when resistance appeared not only to the drugs of choice for first line defense against various infections, but multiple drug resistant strains occurred as well, and, worst of all, resistance began to appear to the handful of antibiotics that were considered drugs of last resort.

• Semi-synthetic drugs had, at first, seemed a viable approach to fighting AMR. Because they were humanly engineered, no ancient mutation existed in the pathogen's gene pool to survive and convey resistance to new generations under antibiotic pressure. Methicillin, a semi-synthetic drug in the penicillin family that was effective against many Gram-positive bacterial infections, was introduced in the 1960s. And yet only a year later, the first case of methicillin-resistant *S. aureus* (*MRSA*) was reported.[50]

• As MRSA spread in hospitals, the much more expensive and toxic vancomycin was found to be effective against it. It interfered with a number of cell wall-building processes, and there were hopes that it would prove too complex for Gram-positive bacteria to fight. But in 1989 the first case of vancomycin-resistant enterococci (*VRE*) infection was identified, and by 1993 VRE had increased to 7.9% of the strains found in American hospitals.[51] In Canada the first outbreak of VRE was in a Toronto hospital in 1995.[52]

• In 1997, the first MRSA strain that was also partially resistant to vancomycin (called *VISA*) was identified in Japan, and shortly afterwards in the United States.[53]

• In July, 2002, the CDC reported a much-feared development – the first case of MRSA that was also completely resistant to vancomycin, as well as oxacillin.

• Two of the limited number of drugs of last resort are Zyvox (with the generic name linezolid, of the synthetic class of oxazolidinones or oxys for short), marketed in 2000, and Synercid, available about six months earlier. Both, however, are very expensive, and by 2001, each

Families of Antibiotics

Antibiotics are often grouped by reference to how they are made. The family of polypeptides, for instance, such as polymixin or bacitracin, are all produced by endospore-forming bacilli. Penicillins are produced by molds.

Antibiotics are also categorized by the way they work. For example, *beta-lactam antibiotics* like penicillin have a specific mechanism to attack the cell walls of Gram-positive bacteria. In general, antibiotics are classed as *narrow spectrum* if they are only effective against either Gram-negative or Gram-positive bacteria. Penicillin is one such example; it is effective against streptococci and staphylococci, but not often against Gram-negatives. *Broad spectrum* antibiotics are effective against both Gram-positives and Gram-negatives. These antibiotics include the cephalosporins; semi-synthetics like ampicillin and methicillin; and the tetracylines, among others. *Limited spectrum* antibiotics are effective against only a single disease-causing species. There are more than 100 commercial antibiotics in use.

had had cases reported that had developed resistance.

• By the late 1990s, strains of food-related illness caused by *Campylobacter* and a virulent strain of *Salmonella* were showing resistance to one of the remaining classes of drugs, the quinolones, that worked against them and other Gram-negatives.

Antibiotic resistance in Canada is, so far, a less extensive problem than in the United States, though it is still higher than in some other developed countries such as Iceland and Denmark. By 2000, MRSA in Canadian hospitals participating in a surveillance program was at over 8% of isolates (i.e., specific strains that were sampled), compared to 50% in some U.S. hospitals. Similarly, VRE prevalence is about 0.5% of isolates in Canadian facilities, whereas the comparable U.S. figure is currently 25%.[54] Nevertheless, the trend toward increasing resistance in Canada has, until recently, been upward, and the difficulties faced by individual patients, doctors, and facilities in outbreaks are severe.

The Costs of Antibiotic Resistance

The most devastating costs of antibiotic resistance are the pain and distress, anxiety, and, in some cases, deaths of patients. Almost as hard to contemplate is the worry and fear of their family members, along with the doctors who watch in frustration as drugs that should work fail. Nor are the effects always confined to the acute infection; permanent impairment of vital organs can occur in some extended illnesses as well. Moreover, every drug-resistant infection is a potential opportunity for resistance genes to be spread among a wider pool of bacteria. And in addition, of course, there are the economic costs.

The economic costs of drug resistance have a number of components. These can include the costs of increased surveillance testing as well as other laboratory costs; the higher costs of alternative drug therapy; and the increased costs of longer hospitalizations. As well, they may include calculated indirect costs of productivity losses due to longer and more severe illnesses and deaths of workers. In the United States, published estimates of the overall costs of antibiotic resistance have ranged from $(US)100 million to $30 billion a year, depending on methodology. One fairly recent study by the National Foundation for Infectious Diseases puts costs in the United States at around $4 billion a year.[55] In Canada, a study published in 2003 in the *Canada Communicable Disease Report* puts the direct costs to the Canadian health system of resistant infections in hospitals at $9-14 million a year more than the costs would have been for non-drug-resistant infections. Screening and precautions to prevent the spread of resistance add a further $26 million/year. However, if the prevalence of drug resistance rises to levels found in U.S. hospitals, added direct expenses could rise to $104-187 million/year, up to nearly $100 million more than if the infections had been drug susceptible.

Appendix A References

44 See *The Killers Within*, Chapter 3, "Early Warning," referenced in End Note 6, for a full discussion of the first warnings and mechanisms of drug resistance in bacteria

45 There is a good discussion of these mechanisms in the web page of howstuffworks, available at http://health.howstuffworks.com/question561.htm

46 Page 173, *The Killers Within*, referenced in End Note 6

47 Information in this paragraph on food-borne illness is from the Union of Concerned Scientists website, available at www.ucsusa.org

48 Information about drug-resistant tuberculosis is available at the American Lung Association website at www.lungusa.org

49 See *The Killers Within*, Chapter 2, "It's A Bug's World," referenced in End Note 6

50 Page 38, *The Killers Within,* referenced in End Note 6

51 Page 45, *The Killers Within,* referenced in End Note 6

52 Referenced in "Antimicrobial Resistance: A Deadly Burden No Country Can Afford to Ignore," prepared by the Canadian Committee on Antibiotic Resistance, published in the Canada Communicable Disease Report, Volume 29-18, 15 September 2003, available at the Public Health Agency of Canada's website at www.phac-aspc.gc.ca/publicat/ccdr-rmtc/03vol29/dr2918eb.html

53 Pages 77-78, *The Killers Within,* referenced in End Note 6

54 These statistics are found in "Antimicrobial Resistance: A Deadly Burden No Country Can Afford to Ignore," referenced in End Note 34

55 These numbers are cited in a report found at the web page for the Center for Science in the Public Interest, found at www.cspinet.org/reports/abiotic.htm

Appendix B: King County, Washington Website List of Endocrine Disrupting Chemicals of Concern

http://dnr.metrokc.gov/WTD/community/edc/chart.htm - Accessed February 2, 2006

The following chart lists endocrine disrupting chemicals that are potentially of concern.

Potential endocrine disrupting chemicals	**What they do and examples of where they're found**
Hormones	
Estrogens, including estrone, estradiol and ethynyl estradiol. Testosterone	Natural and synthetic hormones. Birth control pills containing ethynyl estradiol are one major source of estrogens entering the environment. They're also considered a pharmaceutical.
Industrial chemicals	
Metals	Mercury is found in thermometers, many light switches and some medicines. It's also used in various industrial applications. Cadmium is found in nicad batteries and other industrial uses.
Bisphenol A	This chemical is used to produce epoxy resins and polycarbonate plastics (used commonly in some food and drink packaging).
Phthalates such as	Phthalates have been widely used as plasticizers in many

diethylhexyphthalate	plastics since the 1930s. They are found in plastic wrap, PVC, vinyl flooring, and ink used to print on plastic containers.
Polychlorinated biphenyls (PCBs) and dioxins (PCDDs)	PCBs were used since 1929 in various electrical applications. While no longer used, they can be found in older electrical installations and in marine sediments. Dioxins are produced during paper manufacturing incineration and to produce chlorinated aromatics.
Personal care products	
Phthalates such as diethylhexyphthalate	Phthalates are used in some cosmetics and in some packaging of personal care products.
Alkyphenols such as nonylphenol and octylphenol	These chemicals are mainly used as surfactants in detergents. They can also be used as plasticizers in plastics and UV stabilizers in plastics.
Parabens	This group of chemicals is used as a preservative in many cosmetics, including hand lotions and shampoos.
Pharmaceuticals and over-the-counter drugs	Only a small subset of pharmaceutical drugs are known or suspected of being endocrine disrupting compounds, mainly synthetic steroids and other synthetic hormones (for example, birth control pills, hormone replacement therapy).
Pesticides	
Pesticides, fungicides and herbicides (DDT, lindane, vinclozolin are just a few)	Several chemicals used to control insect pests or weeds in agriculture, landscaping or home gardening have been identified as possible or definite endocrine disrupters.

Alkyphenols	Alkyphenols are often used as carrier solutions for pesticides.

Appendix C: Our Stolen Future Website List of Widespread Pollutants with Endocrine-disrupting Effects

http://www.ourstolenfuture.org/Basics/chemlist.htm - Accessed February 2, 2006

Widespread Pollutants with Endocrine-disrupting Effects

Persistent organohalogens

Compound(s)	Hormone system affected	Mechanism if known	References
Benzenehexachloride (BHC)	Thyroid		Akhtar *et al*. 1996
1,2-dibromoethane	Reproductive		Brittebo *et al*. 1987
Chloroform	Reproductive		Brittebo *et al*. 1987
Dioxins and furans (in order of antiestrogenic potency : 2,3,7,8-tetrachlorodibenzo-p-dioxin > 2,3,7,8-tetrachlorodibenzofuran > 2,3,4,7,8-pentachlorodibenzo-furan > 1,2,3,7,9-pentachlorodibenzofuran > 1,3,6,8-tetrachlo-rodibenzofuran)	Estrogen	work as anti-estrogen through binding with Ah receptor, which then inhibits estrogen receptor binding to estrogen response elements, thereby inhibiting estrogen action	Krishnan and Safe 1993 Klinge *et al*. 1999
Octachlorostyrene	Thyroid		Sandan *et al*. 2000
PBBs	Estrogen/ Thyroid		Bahn *et al*. 1980 Henderson *et al*. 1995
PCBs (in order of antiestrogenic potency: 3,3' -pentachlorobiphenyl > 3,3,4,4,5,5'-hexachlorobiphenyl 3,3',4,4-tetrachlorobiphenyl > 2,3,3',4,4',5'-hexa, 2,3,3',4,4'- and 2,3,4,4',5-pentachlorobiphenyl >	Estrogen/androgen/Thyroid Adverse outcomes in reproductive systems.	Inhibits estrogen binding to the receptor; works as anti-estrogen. anti-androgenic via Ah receptor interaction	Korach *et al*. 1988 Zoeller *et al*. 2000 Grey *et al*. 1999

Aroclors 1221, 1232. 1248, 1254, and 1260 were inactive as antiestrogens at the highest concentrations used in this study (10-6 Ni)			
PCB, hydroxylated	Thyroid	Binds to thyroid hormone binding protein, but not to the thyroid hormone receptor.	Cheek *et al.* 1999
PBDEs	Thyroid	Interfere with thyroxine (T4) binding with transthryetin	Ilonka *et al.* 2000
Pentachlorophenol	Thyroid	Reduces thyroid hormone possibly through a direct effect on the thyroid gland.	Bear *et al.* 1999 Gerhard *et al.* 1999

Food Antioxidant

Compound	Hormone system affected	Mechanism	References
Butylated hydroxyanisole (BHA)	Estrogen	Inhibits binding to the estrogen receptor.	Jobling *et al.* 1995

Pesticide (for information organized by pesticide class)

Compound	Hormone system affected	Mechanism	References
Acetochlor	Thyroid (decrease of thyroid hormone levels, increase in TSH)		Hurley *et al.* 1998
Alachlor	Thyroid (decrease of thyroid hormone levels, increase in TSH)		Wilson *et al.* 1996
Aldrin	Estrogen	Binds to estrogen receptors; competes with estradiol.	Jorgenson 2001
Allethrin, d-trans	Estrogen		Go *et al.* 1999
Amitrol	Thyroid	Thyroid peroxidase inhibitors; inhibits thyroid hormone synthesis.	Hurley *et al.* 1998
Atrazine	Neuroendocrine-pituitary (depression of LH surge), testosterone metabolism.	Inhibits ligand binding to androgen and estrogen receptors.	Danzo 1997
Carbaryl	Estrogen and progesterone		Klotz *et al.* 1997
Chlofentezine	Thyroid	Enhances secretion of thyroid	Hurley *et al.* 1998

		hormone.	
Chlordane	Testosterone and progesterone		Willingham *et al*. 2000
Cypermethrin	Disruption of reproductive function		Moore and Waring 2001
DDT	Estrogen	DDT and related compounds act in a number of ways to disrupt endocrine function by binding with the estrogen receptor, including estrogen mimickry and antagonism, altering the pattern of synthesis or metabolism of hormones, and (4) modifying hormone receptor levels	Soto *et al*. 1994 Lascombe *et al*. 2000 Kupfer *et al*. 1980 Rajapakse *et al*. 2001
DDT Metabolite, p,p'-DDE	Androgen	Inhibits androgen binding to the androgen receptor, androgen-induced transcriptional activity, and androgen action in developing, pubertal and adult male rats.	Kelce 1995
Dicofol (Kelthane)	Estrogen		Vinggaard *et al*. 1999
Dieldrin	Estrogen	Binds to estrogen receptor;competes with estradiol.	Soto *et al*. 1994 Jorgenson 2001
Endosulfan	Estrogen		Soto *et al*. 1994 Soto *et al*. 1995
Ethylene thiourea	Thyroid	Thyroid peroxidase inhibitor.	Hurley *et al*. 1998
Fenarimol	Estrogen	Estrogen receptor agonist.	Vinggaard *et al*. 1999
Fenbuconazole	Thyroid	Enhances secretion of thyroid hormone.	Hurley *et al*. 1998
Fenitrothion	Antiandrogen	Competitive androgen receptor antagonist.	Tamura *et al*. 2001
Fenvalerate	Estrogen		Go *et al*. 1999
Fipronil	Thyroid	Enhances secretion of thyroid hormone.	Hurley *et al*. 1998
Heptachlor	Thyroid		Akhtar *et al*. 1996 Reuber 1987
Heptachlor-epoxide	Thyroid/Reproductive	Metabolite of heptachlor	Reuber 1987

Iprodione	Inhibition of testosterone synthesis		Benhamed 1996
Karate	Thyroid	A decrease of thyroid hormone in serum; direct effect on the thyroid gland?	Akhtar *et al*. 1996
Kepone (Chlordecone)	Estrogen	Displays androgen and estrogen receptor-binding affinities.	Waller *et al*. 1996 Soto *et al*. 1994 McLachlan(ed)
Ketoconazole	Effects on reproductive systems		Marty *et al*. 1999 Marty *et al*. 2001
Lindane (Hexachlorocyclohexane)	Estrogen/Androgen	Inhibits ligand binding to androgen and estrogen receptors.	Danzo 1997
Linuron	Androgen	Androgen receptor antagonist.	Waller *et al*. 1996 Lambright *et al*. 2000 Grey *et al*. 1999
Malathion	Thyroid	Significant decrease of thyroid hormone in serum, with perhaps a direct effect on the thyroid gland.	Akhtar *et al*. 1996
Mancozeb	Thyroid	Thyroid peroxidase inhibitors.	Hurley *et al*. 1998
Maneb	Thyroid	The metabolite ethylenthiourea inhibits thyroid hormone synthesis.	Toppari *et al*. 1995
Methomyl	Thyroid		Porter *et al*. 1993 Klotz *et al*. 1997
Methoxychlor	Estrogen	Through mechanisms other than receptor antagonism. Precise mechanism still unclear.	Pickford and Morris 1999
Metribuzin	Thyroid		Porter *et al*. 1993
Mirex	Antiandrogenic activity; inhibits production of LH. Potentially thyroid.		Chen *et al*. 1986 Chernoff *et al*. 1976
Nitrofen	Thyroid	Structural similarities to the thyroid hormones; nitrofen or its metabolite may have thyroid hormone activities.	Stevens and Summer 1991

Nonachlor, trans-	Estrogen	Estrogen receptor agonist?	Willingham *et al*. 2000
Oxychlordane	Reproductive		Guillette *et al*. 1999
Pendimethalin	Thyroid	Enhances secretion of thyroid hormone.	Hurley *et al*. 1998
Pentachloronitrobenzene	Thyroid	Enhances secretion of thyroid hormone.	Hurley *et al*. 1998
Permethrin	Estrogenic		Go et al. 1999
Procymidone	Androgen	Androgen receptor antagonist.	Ostby *et al*. 1999 Grey *et al*. 1999
Prodiamine	Thyroid	Enhances secretion of thyroid hormone.	Hurley *et al*. 1998
Pyrimethanil	Thyroid	Enhances secretion of thyroid hormone.	Hurley *et al*. 1998
Sumithrin	Androgen		Go *et al*. 1999
Tarstar	Thyroid	A decrease of thyroid hormone in serum; direct effect on the thyroid gland?	Akhtar *et al*. 1996
Thiazopyr	Thyroid	Enhances secretion of thyroid hormone.	Hurley *et al*. 1998
Thiram	Neuroendocrine-pituitary (depression of LH surge), thyroid (decrease of T4, increase of TSH)		Stoker *et al*. 1993
Toxaphene	Estrogen/ Thyroid		Soto *et al*. 1994
Triadimefon	Estrogen	Estrogen receptor agonist.	Vinggaard *et al*. 1999
Triadimenol	Estrogen	Estrogen receptor agonist	Vinggaard *et al*. 1999
Tributyltin	Reproductive		Horiguchi *et al*. 2000
Trifluralin	Reproductive/ Metabolic		Rawlings *et al*. 1998
Vinclozolin	Androgen	Anti-androgenic. (Competes with androgens for the androgen receptor (AR), inhibits AR-DNA binding, and alters androgen-dependent gene expression.)	Soto *et al*. 1994 Soto *et al*. 1995 Kelce *et al*. 1994 Grey *et al*. 1999

Zineb	Thyroid	The metabolite ethylenthiourea inhibits thyroid hormone synthesis.	Toppari *et al.* 1995
Ziram	Thyroid	Inhibits the iodide peroxidase. Structural similarities between ziram and thiram; ziram can be metabolized to thiram in the environment.	Marinovich *et al.* 1997

Phthalate

Compound	Hormones affected	Mechanism	References
Butyl benzyl phthalate (BBP)	Estrogen	Inhibits binding to the estrogen receptor	Jobling *et al.* 1995
Di-n-butyl phthalate (DBP)	Estrogen Androgen	Inhibits binding to the estrogen receptor. anti-androgenic	Jobling *et al.* 1995 Harris *et al.* 1997 Grey *et al.* 1999
Di-ethylhexyl phthalate (DEHP)	Estrogen Androgen	Inhibits binding to the estrogen receptor. anti-androgenic	Jobling *et al.* 1995 Harris *et al.* 1997 Moore *et al.* 2001 Grey *et al.* 1999
Diethyl Phthalate (DEP)	Estrogen		Harris *et al.* 1997

Other Compounds

Compound	Hormones affected	Mechanism	References
Benzophenone	Estrogen	Binds weakly to estrogen receptors, roles of its metabolite remain to be clarified.	Schlumpf *et al.* 2001
Bisphenol A	Estrogen	Estrogenic; binds to estrogen receptor	Fisher *et al.* 1999 Anderson *et al.* 1999 Rajapakse *et al.* 2001
Bisphenol F	Estrogen	Estrogenic; b inds to estrogen receptor	Perez *et al.* 1998
Benzo(a)pyrene	Androgen	anti-androgenic	Thomas 1990
Carbendazim	Reproductive		Gray *et al.* 1990

Ethane Dimethane Sulphonate	Reproductive		Gray *et al*. 1999
Perfluorooctane sulfonate (PFOS)	Thyroid, reproductive	suppression of T3,T4; mechanism unknown	3M data
Nonylphenol, octylphenol	Estrogen	Estrogen receptor agonists; reduces estradiol binding to the estrogen receptor.	Soto *et al*. 1991 Soto *et al*. 1995 Danzo 1997 Lascombe *et al*. 2000 Rajapakse *et al*. 2001
Resorcinol	Thyroid		Lindsay *et al*. 1989
Styrene dimers and trimers	Estrogen	Estrogen receptor agonists	Ohyama *et al*. 2001

Metals

Compound	Hormones affected	Mechanism	References
Arsenic	Glucocorticoid	Selective inhibition of DNA transcription normally stimulated by the glucocorticoid-GR complex.	Kaltreider *et al*. 2001
Cadmium	Estrogenic	Activates estrogen receptor through an interaction with the hormone-binding domain of the receptor.	Stoica *et al*. 2000 Johnson *et al*. 2003
Lead	Reproductive		Telisman *et al*. 2000 Hanas *et al*. 1999
Mercury	Reproductive/ Thyroid		Facemire *et al*. 1995

Appendix D: Environmental Defense Website List of Suspected Endocrine Toxicants

http://www.scorecard.org/health-effects/chemicals-2.tcl?short_hazard_name=endo&all_p=t – Accessed February 2, 2005

Endocrine Toxicants
Exposure to chemical substances can cause adverse effects on the endocrine system, which is comprised of the organs and glands that secrete hormones (Endocrine Toxicity). Hormones control normal physiological processes, maintaining the body's homeostasis. Compounds that are toxic to the endocrine system may cause diseases such as hypothyroidism, diabetes mellitus, hypoglycemia, reproductive disorders, and cancer.

Exposure to endocrine-disrupting chemicals such as polychlorinated biphenyls (PCBs) and DDT have caused a host of toxic effects in wildlife, including impaired reproduction and development. Other endocrine toxicants, such as persistent organochlorine pesticides and dioxins, are being studied for their possible role in promoting hormone-induced cancers (such as breast cancer) and in lowering sperm counts and male fertility.

References used to compile the list of Endocrine Toxicants

Endocrine Toxicity Hazards: suspected

Chemical Name	CAS Registry Number (or EDF Substance ID)	References
ACETOCHLOR	34256-82-1	BKH, WWF
ALACHLOR	15972-60-8	BKH, IL-EPA, JNIHS, KEIT, WWF
ALDICARB	116-06-3	GUIL, JNIHS, KEIT
ALDRIN	309-00-2	IL-EPA, JNIHS
ALKYLPHENOLS	EDF-149	GUIL
ALPHA-ENDOSULFAN	959-98-8	IL-EPA
ALPHA-OXODIPHENYLMETHANE	119-61-9	JNIHS, WWF
1-AMINO-2-CHLOROBENZENE	95-51-2	RTECS
1-AMINO-3,4-DICHLOROBENZENE	95-76-1	BKH
4-AMINO-BENZOLSULFONYL-METHYLCARBAMAT	3337-71-1	RTECS
AMIODARONE	1951-25-3	RTECS

AMIODARONE HYDROCHLORIDE	19774-82-4	RTECS
AMITROLE	61-82-5	BRUC, EPA-SDWA, IL-EPA, JNIHS, KEIT, RTECS, WWF
AMOXAPINE	14028-44-5	RTECS
ANILINE, M-CHLORO-, HYDROCHLORIDE	141-85-5	RTECS
ANTHRACENE	120-12-7	KEIT
AROCLOR 1242	53469-21-9	BKH
AROCLOR 1248	12672-29-6	BKH
AROCLOR 1254	11097-69-1	BKH
AROCLOR 1260	11096-82-5	BKH
ARSENIC	7440-38-2	KEIT, WWF
ARSINE	7784-42-1	RTECS
ATRAZINE	1912-24-9	BKH, GUIL, IL-EPA, JNIHS, KEIT, WWF
Azadirachtin	11141-17-6	JNIHS
BENOMYL	17804-35-2	EPA-SDWA, IL-EPA, JNIHS, KEIT
BENZENE	71-43-2	RTECS
BENZENECARBOPEROXOIC ACID, 1,1-DIMETHYLETHYL ESTER	614-45-9	RTECS
1,2-BENZENEDICARBOXYLIC ACID, DICYCLOHEXYL ESTER	84-61-7	JNIHS
1,2-BENZENEDICARBOXYLIC ACID, DIISODECYL ESTER	26761-40-0	JNIHS
1,2-BENZENEDICARBOXYLIC ACID, DIISONONYL ESTER	28553-12-0	JNIHS
1,2-BENZENEDICARBOXYLIC ACID, DITRIDECYL ESTER	119-06-2	JNIHS
BENZETHONIUM CHLORIDE	121-54-0	RTECS
BENZO(A)PYRENE	50-32-8	KEIT, WWF
BENZYL BUTYL PHTHALATE	85-68-7	BKH, JNIHS, KEIT, WWF
BETA-ENDOSULFAN	33213-65-9	IL-EPA
BETA-LINDANE	319-85-7	IL-EPA, JNIHS, KEIT
BIS(2-ETHYLHEXYL) ADIPATE	103-23-1	JNIHS
BIS(2-ETHYLHEXYL)PHTHALATE	117-81-7	BKH, BRUC, IL-EPA, JNIHS, KEIT, WWF
BIS(TRIBUTYLTIN) OXIDE	56-35-9	BKH, EPA-SDWA, RTECS
BORATES,TETRA,SODIUM SALTS	1303-96-4	RTECS
BROMACIL	314-40-9	EPA-TRI
BROMACIL LITHIUM SALT (2,4(H,3H)-PYRIMIDINEDIONE, ETHYL-3 (1-METHYLPROPYL), LITHIUM SALT)	53404-19-6	EPA-TRI

BROMINE	7726-95-6	EPA-TRI
2-BROMOPROPANE	75-26-3	JNIHS
BUTYLATED HYDROXYANISOLE (BHA)	25013-16-5	JNIHS, WWF
1-BUTYLPROPANE	104-51-8	JNIHS
Bisphenol F	09/02/2467	JNIHS, WWF
C.I. BASIC RED 9 MONOHYDROCHLORIDE	569-61-9	RTECS
C.I. DIRECT BLUE 218	28407-37-6	RTECS
CADMIUM	7440-43-9	IL-EPA, KEIT, WWF
CADMIUM CHLORIDE	10108-64-2	RTECS
CAMPHECHLOR	8001-35-2	BKH, GUIL, IL-EPA, JNIHS, KEIT, WWF
CARBARYL	63-25-2	JNIHS, KEIT, WWF
CARBENDAZIM	10605-21-7	JNIHS, WWF
CARBON DISULFIDE	75-15-0	BRUC, RTECS
CARBON TETRACHLORIDE	56-23-5	RTECS
2-CHLOR-1,3-BUTADIENE	126-99-8	RTECS
CHLORDANE	57-74-9	BKH, IL-EPA, JNIHS, WWF
CHLORDECONE (KEPONE)	143-50-0	BKH, EPA-SDWA, IL-EPA, JNIHS, WWF
CHLORINATED DIPHENYL OXIDE	55720-99-5	BRUC
CHLORINATED PARAFINS (AVERAGE CHAIN LENGTH, C12; APPROXIMATELY 60 PERCENT CHLORINE BY WEIGHT)	108171-26-2	RTECS
CHLORMEQUAT CHLORIDE	999-81-5	RTECS
1-CHLORO-2-NITROBENZENE	88-73-3	RTECS
CHLORODIFLUOROMETHANE	75-45-6	OEHHA-CREL
CHLOROFORM	67-66-3	RTECS, WWF
CHLORPYRIFOS	2921-88-2	KEIT
CIS-CHLORDANE	5103-71-9	IL-EPA
CLOFENTEZINE	74115-24-5	JNIHS, WWF
COBALT CHLORIDE	7646-79-9	RTECS
COPPER (11)-8-HYDROXYQUINOLINE	10380-28-6	RTECS
CYANIDE COMPOUNDS	1073	EPA-HEN
CYCLOSPORIN A	59865-13-3	RTECS
CYPERMETHRIN	52315-07-8	JNIHS, KEIT, WWF
Cobalt sulfate heptahydrate	10026-24-1	RTECS
2,4-D	94-75-7	IL-EPA, JNIHS, KEIT
D-TRANS-ALLETHRIN	28057-48-9	WWF
DDD	72-54-8	BRUC, IL-EPA, JNIHS, KEIT
DDE	72-55-9	BRUC, GUIL, IL-EPA, JNIHS, KEIT, WWF

DDT	50-29-3	BKH, BRUC, IL-EPA, JNIHS, KEIT, RTECS, WWF
DECAHYDRONAPTHALENE	91-17-8	RTECS
DEMECLOCYCLINE	127-33-3	RTECS
DI-N-HEXYLPHTHALATE	84-75-3	BRUC, JNIHS
DI-N-OCTYL PHTHALATE	117-84-0	BRUC, JNIHS
DI-N-PENTYL PHTHALATE	131-18-0	JNIHS
DI-OH-BENZOICACIDS (DHBA)	EDF-374	BRUC
2,4-DIAMINOANISOLE SULFATE	39156-41-7	RTECS
4,4'-DIAMINODIPHENYL ETHER	101-80-4	RTECS
4,4'-DIAMINODIPHENYL SULFIDE	139-65-1	RTECS
DIBENZOFURANS (CHLORINATED)	1080	BRUC, OEHHA-CREL, WWF
1,2-DIBROMO-3-CHLOROPROPANE (DBCP)	96-12-8	IL-EPA, JNIHS, KEIT
1,2-DIBROMOETHANE	106-93-4	JNIHS, WWF
DIBUTYL PHTHALATE	84-74-2	BKH, JNIHS, KEIT, WWF
1,2-DICHLOROBENZENE	95-50-1	RTECS
DICHLOROMETHANE	75-09-2	RTECS
2,4-DICHLOROPHENOL	120-83-2	JNIHS, KEIT
1,2-DICHLOROPROPANE	78-87-5	RTECS
DICOFOL	115-32-2	EPA-SDWA, IL-EPA, JNIHS, KEIT, WWF
DICYCLOPENTADIENYL IRON	102-54-5	RTECS
DIELDRIN	60-57-1	GUIL, IL-EPA, JNIHS, KEIT, WWF
DIETHYL PHTHALATE	84-66-2	JNIHS, WWF
DIETHYLENE GLYCOL MONOMETHYL ETHER	111-77-3	RTECS
DIETHYLSTILBESTROL	56-53-1	IL-EPA
DIFLUBENZURON	35367-38-5	JNIHS, RTECS
DIMETHOATE	60-51-5	BRUC
2,6-DIMETHYL-4-HEPTYLPHENOL, (O AND P)	25154-52-3	JNIHS, WWF
DINITROBUTYL PHENOL	88-85-7	JNIHS
DINITROPHENOLS	25550-58-7	BRUC
DINOCAP	39300-45-3	RTECS
DIPHENYLHYDANTOIN (PHENYTOIN), SODIUM SALT	630-93-3	RTECS
DIPROPYL PHTHALATE	131-16-8	JNIHS
4-DODECYLPHENOL	104-43-8	JNIHS
Dibromoacetic acid	631-64-1	JNIHS
ENDOSULFAN	115-29-7	GUIL, IL-EPA, JNIHS, KEIT, WWF
ENDRIN	72-20-8	IL-EPA, JNIHS
EPICHLOROHYDRIN	106-89-8	RTECS
1-EPOXYETHYL-3,4-EPIXYCYCLOHEXANE	106-87-6	RTECS
ESFENVALERATE	66230-04-4	EPA-SDWA, JNIHS

ETHANOL	64-17-5	RTECS
ETHIOZIN (EBUZIN/TYCOR)	64529-56-2	JNIHS
1-ETHYL-4-HYDROXYBENZENE	123-07-9	JNIHS
ETHYLBENZENE	100-41-4	OEHHA-CREL
ETHYLENE GLYCOL MONOBUTYL ETHER	111-76-2	RTECS
ETHYLENE GLYCOL MONOETHYL ETHER	110-80-5	RTECS
ETHYLENE GLYCOL MONOMETHYL ETHER	109-86-4	RTECS
ETHYLENE THIOUREA	96-45-7	BRUC, JNIHS, OEHHA-CREL, RTECS, WWF
ETOPOSIDE	33419-42-0	RTECS
Ethane Dimethane Sulphonate	EDF-503	WWF
FENARIMOL	60168-88-9	WWF
FENBUCONAZOLE (FENETHANIL)	114369-43-6	WWF
FENITROTHION	122-14-5	WWF
FENOXYCARB	72490-01-8	JNIHS, RTECS
FENVALERATE	51630-58-1	EPA-SDWA, JNIHS, WWF
FERBAM	14484-64-1	BRUC
FIPRONIL	120068-37-3	WWF
FIREMASTER FF-1	67774-32-7	JNIHS, WWF
GAMMA-LINDANE	58-89-9	BKH, JNIHS, KEIT, WWF
HC BLUE 1	2784-94-3	RTECS
HEPTACHLOR	76-44-8	IL-EPA, JNIHS, KEIT, WWF
HEPTACHLOR EPOXIDE	1024-57-3	IL-EPA, JNIHS, KEIT, WWF
1,2,3,4,6,7,8-HEPTACHLORODIBENZO-P-DIOXIN	35822-46-9	IL-EPA
HEXACHLORO-1,3-BUTADIENE	87-68-3	RTECS
HEXACHLOROBENZENE	118-74-1	BKH, BRUC, IL-EPA, JNIHS, KEIT, RTECS
2,2',4,4',5,5'-HEXACHLOROBIPHENYL (PCB-153)	35065-27-1	BKH
3,3'4,4',5,5'-HEXACHLOROBIPHENYL (PCB-169)	32774-16-6	BKH, WWF
1,2,3,4,5,6-HEXACHLOROCYCLOHEXANE (MIXTURE OF ISOMERS)	608-73-1	IL-EPA, WWF
1,2,3,7,8,9-HEXACHLORODIBENZO-P-DIOXIN	19408-74-3	IL-EPA
HEXACONAZOLE (ANVIL)	79983-71-4	JNIHS
HYDRAZINE	302-01-2	OEHHA-CREL, RTECS
HYDROGEN CYANIDE	74-90-8	EPA-HEN, OEHHA-CREL
1-HYDROXY-4-SEC-BUTYLBENZENE	99-71-8	JNIHS
1-HYDROXY-4-TERT-BUTYLBENZENE	98-54-4	JNIHS
2,3,3',4,4',5'-Hexachlorobiphenyl	69782-90-7	WWF
IODINATED GLYCEROL	5634-39-9	RTECS
IODINE	7553-56-2	ATSDR, RTECS
IODINE-131	10043-66-0	BRUC

IOXYNIL	1689-83-4	BRUC
IPRODIONE	36734-19-7	JNIHS, WWF
4,4'-ISOPROPYLIDENEDIPHENOL	80-05-7	BKH, GUIL, IL-EPA, JNIHS, KEIT, RTECS, WWF
KEROSENE	8008-20-6	RTECS
Ketoconazole	65277-42-1	RTECS, WWF
LEAD	7439-92-1	BRUC, IL-EPA, KEIT, WWF
LINURON	330-55-2	BKH, WWF
LITHIUM CARBONATE	554-13-2	RTECS
LORAZEPAM	846-49-1	RTECS
MALATHION	121-75-5	BRUC, JNIHS, KEIT, WWF
MANCOZEB	07/01/8018	BRUC, EPA-SDWA, IL-EPA, JNIHS, KEIT, WWF
MANEB	12427-38-2	BKH, BRUC, IL-EPA, JNIHS, KEIT, WWF
MERCURY	7439-97-6	IL-EPA, KEIT, WWF
MERCURY CHLORIDE (2)	7487-94-7	RTECS
METHAM SODIUM	137-42-8	BKH
METHIMAZOLE	60-56-0	RTECS
METHOMYL	16752-77-5	JNIHS, KEIT, WWF
METHOXYCHLOR	72-43-5	IL-EPA, JNIHS, KEIT, WWF
METHYL PARATHION	298-00-0	IL-EPA, JNIHS
1-METHYL-4-NITROBENZENE	99-99-0	JNIHS
3-METHYLCHLORANTHRENE	56-49-5	BRUC
4,4'-METHYLENEBIS-DIHYDROCHLORIDE BENZENEMINE	13552-44-8	RTECS
2-METHYLLACTONITRILE	75-86-5	NJ-FS
METHYLTHIOURACIL	56-04-2	RTECS
METIRAM	9006-42-2	EPA-SDWA, IL-EPA, JNIHS, KEIT
METRIBUZIN	21087-64-9	JNIHS, KEIT, WWF
MIREX	2385-85-5	BKH, EPA-SDWA, IL-EPA, JNIHS, KEIT, RTECS, WWF
MOLINATE	2212-67-1	JNIHS
MONOCHLOROBIPHENYL	27323-18-8	JNIHS
Methoxyetylacrylate tinbutyltin, copolymer	EDF-501	BKH
Mono-2-ethylhexyl phthalate	4376-20-9	JNIHS
N,N-DIMETHYLANILINE	121-69-7	RTECS
4-N-PROPYLPHENOL	645-56-7	JNIHS
NABAM	142-59-6	BRUC, RTECS
NALIDIXIC ACID	389-08-2	RTECS

1,5-NAPHTHALENEDIAMINE	2243-62-1	RTECS
NICKEL SULFATE	7786-81-4	RTECS
NITROFEN	1836-75-5	EPA-SDWA, JNIHS, KEIT, WWF
NITROGEN DIOXIDE	10102-44-0	RTECS
NONACHLOR, CIS-	5103-73-1	IL-EPA
NONACHLOR, TRANS-	39765-80-5	EPA-SDWA, IL-EPA, JNIHS, WWF
4-NONYLPHENOL	104-40-5	IL-EPA, JNIHS
4-NONYLPHENOL BRANCHED	84852-15-3	JNIHS
2-(2-(2-(2-(NONYLPHENOXY)ETHOXY)ETHOXY)ETHOXY)ETHANOL	9016-45-9	JNIHS
NORETHISTERONE	68-22-4	RTECS
NORFLURAZON	27314-13-2	EPA-TRI
Nifedipine	21829-25-4	RTECS
O,P'-DDT	789-02-6	GUIL
O-CRESOL	95-48-7	RTECS
1,2,3,4,6,7,8,9-OCTACHLORODIBENZOFURAN	39001-02-0	IL-EPA
OCTACHLOROSTYRENE	EDF-151	EPA-SDWA, JNIHS, WWF
OCTYLPHENOXY POLYETHOXYETHANOL	9036-19-5	JNIHS
OCTYLPHENOXYPOLYETHOXYETHANOL	9002-93-1	JNIHS
ORYZALIN	19044-88-3	JNIHS
OXAZEPAM	604-75-1	RTECS
1,1'-OXYBISBENZENE PENTABROMO DERIV.	32534-81-9	ATSDR
OXYCHLORDANE	27304-13-8	EPA-SDWA, IL-EPA, JNIHS, WWF
OXYDEMETON METHYL	301-12-2	JNIHS
OXYPHENBUTAZONE	129-20-4	RTECS
P-CHLOROANILINE.HCL	20265-96-7	RTECS
P-CHLOROPHENYL ISOCYANATE	104-12-1	RTECS
1-(P-HYDROXYPHENYL)OCTANE	1806-26-4	IL-EPA, JNIHS
P-TERT-AMYLPHENOL	80-46-6	JNIHS
PARATHION	56-38-2	EPA-SDWA, IL-EPA, JNIHS, KEIT
PCB, hydroxylated	EDF-507	WWF
PENDIMETHALIN	40487-42-1	JNIHS, WWF
PENTA- TO NONYL-PHENOLS	EDF-194	EPA-SDWA
PENTACHLOROANISOLE	1825-21-4	RTECS
2,3,3',4,4'-PENTACHLOROBIPHENYL (PCB-105)	32598-14-4	WWF
1,2,3,7,8-PENTACHLORODIBENZO-P-DIOXIN	40321-76-4	BKH
2,3,4,7,8-PENTACHLORODIBENZOFURAN	57117-31-4	BKH, WWF
PENTACHLOROPHENOL	87-86-5	ATSDR, BRUC, IL-EPA, JNIHS, KEIT, RTECS, WWF
PERMETHRIN	52645-53-1	EPA-SDWA, JNIHS, WWF

PHENOTHRIN	26002-80-2	JNIHS, WWF
PHTHALATES	EDF-150	GUIL
PICLORAM	01/02/1918	RTECS
POLYBROMINATED BIPHENYLS	PJL335	ATSDR, BKH, BRUC, EPA-SDWA, IL-EPA, WWF
POLYCHLORINATED BIPHENYLS	1336-36-3	BKH, BRUC, GUIL, IL-EPA, JNIHS, KEIT, WWF
POLYCHLORINATED DIBENZO-P-DIOXINS	PCDD	WWF
PROCARBAZINE HYDROCHLORIDE	366-70-1	RTECS
PROCYMIDONE	32809-16-8	JNIHS, WWF
PRODIAMINE (RYDEX)	29091-21-2	WWF
PRONAMIDE	23950-58-5	JNIHS
PROPANIL	709-98-8	RTECS
PROPYLTHIOURACIL	51-52-5	RTECS
PYRIMETHANIL	53112-28-0	WWF
PYRIMINIL	53558-25-1	RTECS
Perfluorooctane sulfonate (PFOS)	EDF-508	WWF
Phenol, 2-[[(tributylstannyl)oxy]carbony	4342-30-7	BKH
QUARTZ	14808-60-7	RTECS
QUINTOZENE	82-68-8	WWF
RESORCINOL	108-46-3	BKH, BRUC, WWF
SIMAZINE	122-34-9	JNIHS
STANNANE, ACETOXYTRIPHENYL	900-95-8	BKH
STRONTIUM (STABLE STRONTIUM CHLORIDE)	10476-85-4	RTECS
STYRENE	100-42-5	BKH, IL-EPA, JNIHS, KEIT, WWF
SULFAMETHAZINE	57-68-1	RTECS
SULFAMETHOXAZOLE	723-46-6	RTECS
SYNTHETIC PYRETHROIDS	EDF-152	EPA-SDWA, JNIHS
Stannane, [1,2-phenylenebis(carbonyloxy)	4782-29-0	BKH
Stannane, tributyl = Tributyltin naphtalate	36631-23-9	BKH
Stannane, tributyl-, mono(naphthenoyloxy	85409-17-2	BKH
Stannane, tributyl[(1-oxo-9,12-octadecad	24124-25-2	BKH
Stannane, tributyl[(1-oxo-9-octadecenyl)	3090-35-5	BKH
Stannane, tributyl[[[1,2,3,4,4a,4b,5,6,1	26239-64-5	BKH
2,4,5-T	93-76-5	IL-EPA, JNIHS, KEIT
T-2 TOXIN	21259-20-1	RTECS
TEFLUTHRIN	79538-32-2	WWF
3-TERT-BUTYLPHENOL	585-34-2	JNIHS
2,2',6,6'-TETRABROMO-4,4'-ISOPROPYLIDENEDIPHENOL	79-94-7	JNIHS
2,2',4,4'-TETRACHLOROBIPHENYL (PCB-47)	2437-79-8	BKH
3,3',4,4'-TETRACHLOROBIPHENYL (PCB-77)	32598-13-3	BKH, RTECS, WWF

2,3,7,8-TETRACHLORODIBENZO-P-DIOXIN (TCDD)	1746-01-6	BKH, BRUC, IL-EPA, JNIHS, KEIT, OEHHA-CREL, RTECS, WWF
2,3,7,8-TETRACHLORODIBENZOFURAN	51207-31-9	IL-EPA, JNIHS, RTECS, WWF
TETRAHYDROFURAN	109-99-9	RTECS
(1,1,3,3-TETRAMETHYLBUTYL)PHENOL	27193-28-8	JNIHS
4-(1,1,3,3-TETRAMETHYLBUTYL)PHENOL	140-66-9	JNIHS
TETRASUL	2227-13-6	RTECS
THEOBROMINE	83-67-0	RTECS
THEOPHYLLINE	58-55-9	RTECS
THIAZOPYR (MON 13200)	117718-60-2	WWF
THIOCYANATE	EDF-058	BRUC
THIOPHANATE ETHYL	23564-06-9	EPA-TRI
THIOPHENE	110-02-1	RTECS
THIRAM	137-26-8	BKH, WWF
TOLBUTAMIDE	64-77-7	RTECS
TRANS-CHLORDANE	5103-74-2	KEIT
TRIADIMEFON	43121-43-3	WWF
TRIADIMENOL (BAYTAN)	55219-65-3	WWF
TRIBUTYLTIN	688-73-3	BKH, IL-EPA, WWF
TRIBUTYLTIN BENZOATE	4342-36-3	BKH
TRIBUTYLTIN COMPOUNDS	EDF-184	BKH
TRIBUTYLTIN FLUORIDE	04/10/1983	BKH
TRIBUTYLTIN METHACRYLATE	2155-70-6	BKH
TRICHLOROETHYLENE	79-01-6	EPA-HEN
TRIFLURALIN	1582-09-8	IL-EPA, JNIHS, KEIT, WWF
TRIPHENYLTIN	668-34-8	BKH
Tarstar	EDF-506	WWF
Tetrachloro DDT = 1,1,1,2-Tetrachloro-2,2-bis(4-chlorophenyl)ethane	3563-45-9	BKH
Tri-n-propyltin (TPrT)	2279-76-7	BKH
Tributyltincarboxylate	EDF-499	BKH
Tributyltinnaphthalate	26636-32-8	BKH
Tributyltinpolyethoxylate	EDF-500	BKH
1,2,3-Trithian-5-amine, N,N-dimethyl-, ethanedioate (1:1)	31895-22-4	RTECS
Urea, N,N-dimethyl-N'-(3-chloro-4-methoxyphenyl)-	19937-59-8	RTECS
VINCLOZOLIN	50471-44-8	BKH, EPA-SDWA, EPA-TRI, GUIL, IL-EPA, JNIHS, KEIT, WWF
VM & P (VARISH MAKERS & PAINTERS) NAPHTHA	8030-30-6	RTECS
ZINEB	12122-67-7	BKH, BRUC, EPA-SDWA, IL-EPA,

		JNIHS, KEIT, RTECS, WWF
ZIRAM	137-30-4	EPA-SDWA, JNIHS, KEIT, WWF
3'-methyl-4-dimethylaminoazobenzene	55-80-1	RTECS
2,3,4,4',5- pentachlorobiphenyl	EDF-505	WWF
1,2,3,7,9-pentachlorodibenzofuran	EDF-502	WWF
pentamidine	140-64-7	RTECS
2-propenoic acid, 2-methyl-, methyl ester = Stannane, tributylmeacrylate	26354-18-7	BKH
1,3,6,8-tetrachlo-rodibenzofuran	EDF-504	WWF

Appendix E: Pharmaceuticals and EDS References

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