centres of excellence *for* WOMEN'S HEALTH

RESEARCH BULLETIN

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NEW QUESTIONS NEW KNOWLEDGE

INSIDE

Safety First: Women and Health Protection

This issue of the Research Bulletin *features the contributions of Women and Health Protection, formerly known as the Working Group on Women and Health Protection. This group is supported in part by the Women's Health Contribution Program of Health Canada and is composed of researchers, health providers, educators, and consumers interested in policy-directed research and public education on health protection issues. I am pleased to welcome Anne Rochon Ford, Coordinator of Women and Health Protection, as guest editor. As you will learn in this issue, women in Canada have had an alarming history with respect to pharmaceutical products and medical devices. The articles that follow caution regulators, consumers, practitioners, and researchers to learn from the past in order to protect women's health in the future.*

~ Ann Pederson, Editor

BOTH WOMEN AND MEN, YOUNG AND OLD, suffer the ill effects of drugs and medical devices that are inadequately tested and then insufficiently monitored once they are released. However, on closer examination, it would seem that women have been the proverbial canaries in the coal mine when it comes to the safety of drugs and medical devices in Canada. Consider the dubious legacy. DES (diethylstilbestrol), a hormone drug, was known to cause serious reproductive problems in animals as early as the 1930s, and was shown to be ineffective in preventing miscarriage in women by the mid-1950s. Yet it was prescribed to pregnant women until the early 1970s when serious cancers and other reproductive problems began to be identified in the daughters and sons of women who had taken DES.

In the 1970s, the Dalkon Shield intra-uterine contraceptive device was found to cause infertility and life-threatening uterine infections only after it had been approved for marketing. In the late 1980s, the Meme breast

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The legacy that began with DES *can* stop here.

cont'd

implant was associated with questions about serious systemic complications and ev entually r emoved fr om the mar ket. Women's health and disability adv ocates raised concerns about injectible and implanted contraceptiv es, such as Depo-Provera and N orplant, soon after mar keting had begun, but warnings about harmful effects w ere only issued years later after millions of women worldwide had used them. M ost r ecently, in 2002, the finding that harm outweighs benefit with long-term use of hormone replacement therapy, comes after millions of women w ere prescribed hormones and before research had proved efficacy and long-term safety . There is incr easing evidence for concern that harmful effects to animals from estrogens in the environment may also translate into human harm.

This issue of the *Research Bulletin* highlights some ways that women's health researchers and advocates are working to try to avoid having history repeat itself. Penny Van Esterik of the National N etwork on E nvironments and Women's H ealth offers a balanced perspectiv e about the warnings r elating to breast milk and envir onmental contaminants. R esearchers affiliated with the B.C. Centr e of E xcellence for Women's Health, furthering the innovative work of Ruth Cooperstock from the 1970s, describe the continuing pr oblem of o ver-prescription of benz odiazepines to women. Ann P ederson and Aleina Tweed, also of the B.C. Centr e, present the case for the cr eation of a br east implant r egistry to aler t women to, and gather evidence about, health pr oblems associated with these devices. Women and H ealth P rotection, backed with evidence from research by Barbara Mintzes, calls upon Health Canada's Health Products and Food Branch to resist pressure to appr ove dir ect-to-consumer adv ertising of prescription dr ugs and warns of concerns about harmful drugs like D iane-35. Their message to our legislators is clear—put safety , not pr ofit, first, and adher e to the precautionary principle. As S haron B att notes else where in this issue: "The widespread myths about hormone therapy were based, not on science, but on marketing that subverted science". She argues forcefully for the need to be looking not to pharmaceuticals but to some of the fundamental tenets of public health—clean air, healthy wor kplaces, and the social determinants of women's health—for disease prevention.

Colleen F uller draws attention to shor tcomings in our current post-mar ket dr ug sur veillance system. Women's particular susceptibilities to drug-related health risks must be taken into consideration by Canada's adverse drug reactions reporting program. In an ar ticle about Canada's role in the process of the I nternational H armonisation of Pharmaceuticals, Women and H ealth P rotection, using original work done by John Abraham, again urges that safety standards be paramount and the par ticular needs of women and other groups are not lost.

The legacy that began with DES *can* stop here. Our national policy-makers have not only the r esponsibility but the tools at hand to transform our health pr otection system, making it one that is mor e r esponsive to women 's health, and ensuring better health for all. Any proposed legislation and regulations should undergo a gender-based analysis and conform to the federal go vernment's "Plan for G ender Equality" and "Health Canada's Women's Health Strategy". What is needed is the political will to make these changes.

Anne Rochon Ford
Coordinator, Women and Health Protection

The Steering Committee of Women and Health Protection consists of Sharon Batt, Madeline Boscoe, Anne Rochon Ford (ex officio), Dr. Joel Lexchin, Dr. Abby Lippman, Carla Marcelis (ex officio), Dr. Fiona Miller, and Barbara Mintzes.

SAFETY AND THE PRECAUTIONARY PRINCIPLE

Hormone Therapy: Health Protection Lessons from the Women's Health Initiative

Sharon Batt, Elizabeth May Chair in Women's Health and the Environment at the Atlantic Centre of Excellence for Women's Health, Dalhousie University and Women and Health Protection

In July 2002, the American researchers conducting the Women's Health Initiative (WHI) halted their large clinical trial to evaluate menopausal hormone therapy (HT). Rather than preventing diseases in aging women, as many had claimed, the study found that a drug called Prempro (estrogen + progestin) actually increases a woman's risk of heart disease (heart attacks, strokes, and blood clots) and breast cancer—the two most common causes of death in post-menopausal women.[1]

Hormone therapy—unsafe pills being promoted as a disease preventative for women—fits a familiar pattern: from 1941 to 1971, DES (diethylstilbestrol), a cancer-causing drug, was prescribed to women in Canada and the United States to prevent miscarriage; today, raloxifene and tamoxifen are being tested as preventives for breast cancer in spite of links to blood clots and increased risk of endometrial cancer.[2] Over a period of decades, the drug regulatory system in both countries has allowed misinformation to spread and be translated into dangerous medical practice.

Prevention pills are different from those prescribed for treatment; they require a stronger health protection policy framework. The lessons of health protection that are described in this article are drawn from the WHI—an exemplary clinical trial to study disease prevention in women.

Lesson One: The standard of safety for prevention interventions must be higher than for disease treatment.
The WHI illustrates the contrasting approaches of disease prevention and disease treatment. One approach targets healthy populations, the other helps suffering individuals. To explain why the WHI study was halted, one of the study's Principal Investigators said, "We have a higher standard [of safety] for prevention."[3] Many people thought that the researchers had over-reacted: increase in the risk that any one woman in the trial would develop breast cancer or heart disease because of HT appeared to be relatively small. In fact, by the safety standards of public health where many thousands of people are exposed, these risks were so high that the Principal Investigators agreed, "There's no role for HT in disease prevention."[4]

Lesson Two: Disease prevention requires a holistic model of health.
The WHI used a holistic model of health to scientifically address the phenomenon of "disease substitution", where a drug reduces the risk of one disease while increasing the risk of others. This meant that the trial would be stopped if global risks exceeded global benefits, or vice versa. By July 2002, the significantly increased risks for breast cancer (expected) and heart disease (unexpected) overwhelmed the benefits for bone loss (expected) and colorectal cancer (unexpected).

Lesson Three: Long-term clinical trial data are essential before drugs are promoted for prevention, but few drugs warrant a clinical prevention trial. Market forces should not determine which drugs are tested for prevention.
Collecting definitive clinical trial data on prevention is much more expensive than collecting comparable data for treatment: the number of volunteers needed is enormous and the trials must run for many years. Before its launch, critics opposed the WHI as "too expensive" and "unethical"—because women in the control group would be denied the presumed protection of HT against heart disease.

Post-menopausal use of hormones for disease prevention had to be tested in a clinical trial because the practice of doctors prescribing the drugs to women had already taken hold, even though long-term safety and efficacy were not established. Clearly, drugs should be tested *before* claims are made and prescriptions written.

The Principal Investigators of the WHI argue, convincingly, that further trials to test other estrogen + progestin formulations and doses would be both unethical and a poor use of tax dollars because there is no reason to believe other HT formulations would have a different result. Similarly, there is no reason to test HT drugs for the prevention of cardiovascular disease in women 50-59 years old; one third of the WHI's volunteers were in their 50s and they had the highest increased risk of stroke.[5]

Classic public health strategies —clean air and water, nutritious food, adequate housing, and safe workplaces— prevent many diseases and cause none. A very few medications meet the stringent requirements of public health: vaccinations for common childhood diseases, anticoagulants to prevent blood clots in surgery, and Pepto-Bismol for travellers' diarrhea, are exceptions to the rule.

Lesson Four: Curb the pervasive industry influence that contributes to irresponsible drug promotion and off-label prescribing.
The widespread myths about HT were based, not on science, but on marketing that subverted science. The American physician Robert Wilson planted the early seeds in 1965 with his book *Feminine Forever*. Wilson concealed the fact that he was a consultant to the manufacturer of Premarin while he flogged his popular book. In the mid-1970s a clinical trial showed that Premarin increased the risk of endometrial cancer, and a blue-ribbon scientific panel rejected virtually all claims for estrogen replacement therapy except for the alleviation of hot flashes and vaginal dryness.[6] When sales fell, manufacturer Wyeth-Ayerst added progestin to the estrogen pill, creating Hormone Replacement Therapy (HRT).

The new drug countered the increased risk of endometrial cancer, but did nothing to slow the runaway claims about the preventative benefits of HRT. Articles like "Hormone Replacement Therapy for All? Universal Prescription is Desirable"[7] ran in respected medical journals, and obstetrician/ gynecologists' organizations recommended that all post-menopausal women take hormone replacement therapy for disease prevention. Conflicts of interests affect medical prescribing generally; however, preventative drugs are particularly attractive candidates for the phenomenon known as the medicalization of health.

Lesson Five: Take regulatory action to curb medicalization of normal conditions like menopause.
Menopausal estrogen and combined hormonal pills were marketed to physicians and women on the grounds that menopause is a disease caused by hormone "deficiency". The terms "estrogen *replacement* therapy" (ERT) and "hormone *replacement* therapy" (HRT) reflect this misogynist construction of menopause as a disease, rather than a normal transition in women's lives.

Following the announcement of the WHI study results, the US Food and Drug Administration (FDA) formally adopted the term "menopausal hormone therapy" (HT) to replace the term HRT. The change signals that hormone therapy should be considered cautiously and only for short-term symptom relief during menopause.

Lesson Six: Track and curb off-label preventative drug use separately from indicated treatment uses for the same drug.
Physicians can prescribe drugs for non-indicated ("off-label") use. While this practice may be justified in exceptional individual cases, HT illustrates the danger when off-label prescribing becomes routine. Health Canada's post-approval surveillance system does not distinguish short-term use of the drug for indicated symptoms, like hot flashes, from long-term use. In the absence of such tracking, we will probably never know how many women have died from iatrogenic endometrial cancer, heart disease, or breast cancer.

Clearly, drugs should be tested *before* claims are made and prescriptions written.

Without the leadership of organizations independent of the drug industry, HT would have been used far more widely than it was.

Lesson Seven: Support advocacy by organizations that are independent from industry and curb the influence of groups and individuals that receive funds from companies whose products they promote.

Women's health advocates and organizations have protested the unsubstantiated claims for HRT since the 1970s. Without the leadership of organizations independent of the drug industry, HT would have been used far more widely than it was. The National Women's Health Network (NWHN) in the United States successfully fought for patient package inserts for all estrogen products, a move which the American College of Obstetricians and Gynecologists challenged in a court action.[8] The NWHN also opposed a 1990 Wyeth-Ayerst application to the FDA to have ERT approved for prevention of heart disease, and lobbied to have the WHI study funded.[9]

Independent public interest groups in Canada and abroad are among the few voices opposing the industry-driven system of physician education and clinical research and the exaggerated claims about the benefits of drugs in direct-to-consumer ads. However, Canadian policies restrict public input into drug policy formation through tax laws that limit advocacy by non-profit groups and through maintenance of secrecy in the drug regulatory process.

Conclusion

Canada's current health policies nourish the rapid development and dissemination of preventive drugs, but provide few checks on their over-promotion. The results of the WHI challenge these biased health policies. The experience of hormone therapy is a cautionary tale to Canadians engaged in the renewal of health protection policies and our health care system.

NOTES

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SAFETY AND THE PRECAUTIONARY PRINCIPLE

Registering the Impact of Breast Implants

Ann Pederson, British Columbia Centre of Excellence for Women's Health, and Aleina Tweed, British Columbia Centre of Disease Control

Breast implants are used for breast augmentation, breast reconstruction (for example, following mastectomy), and/or revision (replacement) of an existing implant. In Canada an estimated 100,000 to 200,000 women have breast implants.[1] Approximately 80% of these surgeries are for breast augmentation, while the remaining 20% are for reconstruction after cancer or prophylactic mastectomy or to correct under developed or non-developed breasts.[2] While most women are typically pleased with the results of their breast implant surgery, others feel that implants have compromised their short- and long-term health. [3] Recent reports indicate that the rates of localized complications and repeat surgeries following breast implantation are high and the long-term effects remain unknown.[4] Although many studies have found no association between breast implants and systemic complications such as autoimmune or connective tissue diseases, [5] the fact that implant removal frequently produces a reversal of symptoms in women who suffer from them continues to raise questions about a causal link. [6]

To ensure that breast implants are not causing harm, systematic documentation and the development of a credible evidence base on the effects of breast implants are scientifically and ethically necessary. The key to such credible information is the establishment of a registry for women with breast implants.

While there are some American data on the number of procedures performed, Canadian plastic surgery and/or medical organizations do not track even crude numbers. In both countries, the absence of mechanisms to track patients over time and across jurisdictions further hampers efforts to document the impact of cosmetic surgery. And while many health care procedures can be investigated in Canada through an examination of public administrative records, most cosmetic surgery is financed privately and isn't recorded in public databases. This means that analysts face significant challenges when conducting assessments, and consumers and policy makers have a very limited evidence base for decision making.

The United States, Australia, Denmark, and the United Kingdom have established national breast implant registries for the purposes of identification, health protection, and research. In Canada, researchers, policy advisors, and women with breast implants have called for authorities to take similar action.[7] Canada is in a position to benefit from the experiences of these countries; the registry in United Kingdom provides an important case in point.

In response to a recommendation by the Department of Health's Independent Expert Advisory Group, in July 1993, the United Kingdom was the first country in the world to establish a national registry. Consisting of a prospective and retrospective registry covering both private and National Health Service activities, the aim of the National Breast Implant Registry (NBIR) in Odstock Hospital in Salisbury is to establish a cohort for studies of breast implantation and its associated effects. (Information in the registry is subject to the national Data Protection Act.) A pilot study using NBIR data is now underway.[8]

Key features of the NBIR are:

- Participation is voluntary: There is no legislative basis for either the registry itself or for patient registration. Data collection is therefore contingent upon patient consent and physician cooperation.
- Multi-centre participation: Initial registrants were identified from hospital operating theatre departments, individual plastic surgeons, and patient groups. Currently, some 280 centres report to the registry, with about 30 centres conducting 80% of the surgeries.
- Basic information collection: The registry collects demographic information, identifies the type of implant, the anatomical location of the implant (above or below

the pectoral muscle), and the main indications for the operation.

- Multi-procedure recording: Implantations and explantations (removal of the implant) are registered.
- Anonymity: Surgeons are not identified.
- Low cost: The ongoing cost of this registry is modest (approximately £25,000 per year), recording approximately 12,000 surgeries per year.

The British government's recall of the Trilucent™ breast implant in 2000 illustrates the usefulness of the NBIR. Through the registry, thousands of women were notified of the manufacturer's concerns about leakage of the implant filler, based on soybean oil, that could potentially produce toxic components. The government advised women to have their implants removed or replaced. If the registry did not exist, the only mechanisms that would have been available to advise women of the medical directive would have been the mass media and individual practitioners.

A registry alone will not answer all of the questions surrounding the safety of breast implants. As the case of the British registry demonstrates, it is a strategy that has been proven to work quickly and efficiently to protect women's health.

For a copy of the full report, *Registering the Impact of Breast Implants*, contact:

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NOTES

1. In the USA more than 200,000 breast augmentations were performed in 2000 alone. See the American Society of Aesthetic Plastic Surgeons at http://www.surgery.org. Comparable Canadian data are not available, although the Canadian Society of Plastic Surgeons (http://www.plasticsurgery.ca) suggests that Canadian numbers would be one tenth of those in the United States.

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SAFETY AND THE PRECAUTIONARY PRINCIPLE

Women and Adverse Drug Reactions: Reporting in the Canadian Context

Colleen Fuller, PharmaWatch and Women and Health Protection

An effective system of reporting and monitoring adverse drug reactions (ADRs) is vital to any strategy designed to support and improve women's health. The first study of the Canadian system, by Women and Health Protection, concludes that reporting arrangements within Canada's health protection system are weak, under funded, and inadequately supported at the political level within Health Canada. Highlights from the report, *Women and Adverse Drug Reactions: Reporting in the Canadian Context* (2002), are described in summary form here.

In the 1960s the modern women's health movement arose out of a feminist critique of the medical industry as an institution of social control over women. Women began to organize and demand changes in the way medicine was practised, arguing that physicians, in particular, ignored problems that were experienced mainly or exclusively by women. A case in point was DES (diethylstilbestrol), a synthetic hormone developed in 1938 and prescribed to an estimated 200,000 to 400,000 Canadian women to prevent miscarriage. Thirty years later, DES was linked to a number of health problems in daughters exposed to the drug in the womb, including reduced fertility, complications in pregnancy, and a rare form of vaginal cancer.[1]

While the inadequacies in the drug safety and post-market surveillance systems affect all communities, women's experiences with DES—as well as thalidomide in the 1960s, the Dalkon Shield and the Meme breast implant in the late 1980s—underscored the link between sex and gender and the safety of drugs and medical devices. These disasters also contributed to a growing interest in health protection and prescription medicines on the part of the general public and health advocates. It was apparent that the gender biases in the health sector, already identified by women and many consumer advocates, were also undermining the ability of Canada's system of health protection to serve the needs and interests of women and girls.

What is the significance of this bias for the current system of reporting adverse drug reactions? Evidence is mounting that women are at greater risk than men are for adverse drug reactions that take place in both community and hospital settings.[2] Female patients are estimated to have a 1.5 to 1.7-fold greater risk of developing an adverse reaction to drugs compared with male patients. [3] The reasons are not wholly understood, but the differences cannot be attributed solely to patterns of use, for example, higher rates of prescription drug use or multiple drug therapy.[4] According to a recent report of the US General Accounting Office (GAO), 8 of the 10 prescription drugs withdrawn between 1997 and 2001 posed greater health risks for women than for men. [5] One reason may have been due to a higher level of prescription drug use among women. But the GAO concluded that a significant number of the drugs that were withdrawn may have posed greater health risks for women because of "physiological differences that make women differentially more susceptible to some drug-related health risks".[6]

A number of strong, positive initiatives have taken place within Health Canada to support strategies that enhance women's health —including the Women's Health Bureau, the implementation of a gender-based analysis, and the federal government's "Plan for Gender Equality". But in the area of drug-related health risks to women, these efforts are undermined by a system of post-market drug safety that is inadequately funded and supported.

Canada's System of ADR Reporting

Clinical trials are the first stage of Canada's drug regulation system, followed by the drug approval stage, and promotion and post-market monitoring. Post-market surveillance in Canada is the weakest stage of drug regulation, with the lowest budget.

At the end of the 1980s and throughout the 1990s a series of crises and scandals, including those related to the Dalkon

Shield, the Meme breast implant, and tainted blood, made it clear to most Canadians that the health protection system was in need of major reform. Indeed, no other part of Health Canada has come under such intense public scrutiny as the health protection system. In April 2002 a new branch—the Marketed Health Products Directorate (MHPD)—was established as part of a massive reorganization of the health protection system.

The MHPD has a much broader range of responsibilities than any of its predecessors, with a mandate to monitor pharmaceuticals, biologicals, vaccines, medical devices, natural health products, radiopharmaceuticals (medicinal products that are radioactive when used in patients), and veterinary drug products. The MHPD is charged with monitoring and collecting adverse reaction and medication incident data, reviewing and analyzing product safety data, conducting risk/benefit assessments of marketed health products, communicating product related risks, and monitoring regulated advertising activities. Yet the MHPD was provided an initial allocation of only 35 scientific staff, 15 support staff, and a budget of only $10 million annually.[7]

Health Canada has established a toll-free consumer ADR reporting line and the Canadian ADR Monitoring Program publishes a newsletter available on-line to the public. While these efforts are welcome—and are contributing to increased reporting—much more is needed to increase awareness about Canada's system of reporting adverse drug reactions. There are few incentives to enhance reporting by physicians, pharmacists, and manufacturers, and consumers and patient advocacy groups face significant barriers to reporting, beginning with, for example, the lack of promotional efforts to support the use of the toll-free consumer reporting line. Education is needed, not only of the public, but of health professionals, about the contribution they can make to the safer use of prescription drugs.

Without an adequately staffed and funded mechanism to systematically collect, investigate, analyze, and interpret data on adverse reactions that may be associated with drug therapy or medical devices, efforts to develop an effective public health policy for women are inevitably undermined. Of equal importance is a political commitment by Health Canada to design a system of adverse drug reaction reporting that will fully serve the health needs of women.

We urge Health Canada to consult with the women's health community to develop a comprehensive strategy for post-market surveillance of women's experiences with prescription drugs. Reform in this area must embrace the fundamental principle of the right of Canadians to be warned and informed about the medicines they use.

For a full copy of *Women and Adverse Drug Reactions: Reporting in the Canadian Context,* contact:

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NOTES

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PUBLIC HEALTH vs. PROFIT

Direct-to-Consumer Advertising of Prescription Drugs – Whatever the Problem, You Can Always Pop a Pill

Barbara Mintzes, Centre for Health Services and Policy Research, University of British Columbia, and Women and Health Protection

A billboard at a bus shelter shows an attractive brown-skinned young woman, with the caption, "A lesson in first impressions… Always leave something to the imagination. Be mysterious." Alesse is the name of the drug printed below with an image of the 21-day birth control pill pack. A television ad for a hormonal acne drug shows young girls with beautiful skin dancing to pop music and preening in front of a mirror. The ad ends with the drug name, Diane-35.

These are recent Canadian prescription drug ads. The messages vary but both are aimed at women and include advice about gender roles: take medicines to be blemish-free, or to be "mysterious", which means quietly assuming sole responsibility for birth control.

Prescription Drugs Advertising to the Public

The United States and New Zealand are the only countries to allow direct-to-consumer advertising of prescription drugs (DTCA). Spending on DTCA in the U.S. has grown rapidly, reaching U.S. $2.5 billion in 2000.[1] Since late 1997, when the U.S. Food and Drug Administration (FDA) eased regulatory restrictions, television advertising has grown dramatically.

DTCA is not currently allowed under Canada's Food and Drugs Act, except for "name, price and quantity", a 1978 amendment allowing comparative price advertising. However, the federal government is considering legislative change to introduce DTCA, and Canadians are increasingly exposed to cross-border advertising from the U.S. as well as to Canadian ads of questionable legality, such as those described above.

Canada is not alone in reviewing its legislation: Australia, the European Union, and South Africa have also considered introduction. DTCA is controversial, with many claims made about benefits and harm. Proponents say that it educates and empowers patients, improves compliance and leads to earlier medicine use, better health, and fewer hospitalizations. Critics raise concerns that it stimulates unnecessary and inappropriate drug use, interferes with doctor/patient relations, and leads to increased drug costs.

What Do We Know About Effects of DTCA?

A U.S. congressional research agency summarized the results of surveys of random samples of the U.S. public, estimating that 8 million Americans request and receive a prescription for an advertised drug each year.[2] Consistently, American consumer surveys show that someone who asks for an advertised medicine usually gets it.[3]

An FDA survey asked doctors about their last patient who had requested an advertised drug.[4] Over a quarter felt somewhat or very pressured to prescribe and fewer than half reported no pressure. In another study of 1,400 consultations in family doctors' offices in Vancouver and Sacramento, three-quarters of patients who asked for an advertised drug received a prescription, although doctors only judged this to be a "very likely" choice for other similar patients half the time.[5]

In both the U.S. and New Zealand, regulatory violations are common, mainly due to inadequate provision of risk information.[6] Over 90 U.S. DTCA campaigns were found to violate U.S. law between 1997 and 2001 and repeat violations were common.[7]

A 10-year review of ads in 18 major U.S. magazines found that most ads omitted key information needed for informed health care choices. Nine out of 10 failed to say how likely a treatment was to work and seven out of ten mentioned no other possible treatments.[8] A 1998-1999 study found that nearly nine out of 10 ads described benefits only in vague, emotional terms,[9] and that nearly one-quarter offered financial incentives such as free trial offers. In sex-specific ads, women are targeted more than twice as often as men[10] and

Little is known about longer-term or less common risks of the newest drugs, raising questions about the public health impact of stimulating widespread use.

the volume of DTCA is highest in women's magazines.[11]

Around 40% of spending on DTCA is on just 10 products each year.[12] These are generally new, expensive drugs for long-term use by large target audiences. The choice is a marketing decision. Drugs for baldness, runny nose, and toenail fungus are all heavily advertised, whether or not these are pressing public health concerns.

Little is known about longer-term or less common risks of the newest drugs, raising questions about the public health impact of stimulating widespread use. Several drugs later withdrawn for safety reasons have been advertised to the U.S. public, including the diabetes drug Rezulin, which was named as the suspected cause in nearly 400 deaths before its March 2000 withdrawal.[13]

Advertised drugs are linked to rapidly escalating U.S. drug costs. The 25 drugs with the highest advertising spending in 1999 were responsible for over 40% of the U.S. $17.7 billion increase in spending on drugs in 1999 as compared to 1998.[14]

In summary, there is evidence that DTCA affects patient behaviours, prescribing decisions, and drug costs. The educational value of DTCA is inadequate for informed choice, but doctors usually prescribe a drug if a patient requests it. No research has been done on effects on health, hospitalization rates, serious illness, or mortality.

No New Legislation, But a Dramatic Shift in Policy

In March 2002 the federal Health Minister announced that the government would not introduce DTCA. However, recent policy changes had already opened the door to many "made-in-Canada" ads.

Women and Health Protection made a complaint about ads for Alesse, a birth control pill, in May 2000. In November 2000, Health Canada published a policy paper in response, saying that it was illegal to run two similar ads, one saying the drug's name, the other talking about its use, in the same media.[15] This paper implies that it is legal to advertise just the drug name ("reminder" ads) or the approved use ("help-seeking" ads), but not both. The justification given is the 1978 price-advertising clause. This is consistent neither with the public health aims of prohibiting prescription drug advertising to the public, nor the 1978 clause, which prohibits all representations other than name, price, and quantity.

Some of the most blatant DTCA campaigns in Canada target young women. In March 2001, Women and Health Protection made another complaint about ads for Diane-35, a drug approved in 1998 in Canada to treat severe acne. This drug had been used for birth control in Europe, but its use was restricted to acne in 1995 because of liver toxicity.[16] New Zealand, the U.K., and Canada have posted warnings of risks of potentially fatal blood clots.[17] Health Canada has not informed us of any action taken in response to this complaint beyond referring it to another department. The ads, which target teenaged girls, were still running months later and the drug is increasingly being prescribed for birth control.

Debates on DTCA in Canada tend to focus on whether full U.S.-style DTCA should be allowed, not on current enforcement of the law. If the Act has loopholes that make no sense from a public health perspective, we need clarifying language introduced. We also need publicly accountable

enforcement procedures, including active monitoring and escalating fines and sanctions to prevent future violations.

DTCA sends a powerful message: whatever the problem, no matter how minor, you can always pop a pill. The Canadian public needs access to up-to-date, accurate, comparative information about all treatment options, drug and non-drug, independent of vested financial interests. Advertising aims to sell a product and has quite a different message.

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PUBLIC HEALTH vs. PROFIT

International Harmonisation of New Drugs Regulation: Not in Women's Best Interest

Women and Health Protection, based on a paper by John Abraham, Professor, Centre for Research in Health and Medicine, University of Sussex, Brighton

For the last 12 years, a pharmaceutical industry/government organization called the International Conference on Harmonisation of Technical Requirements (ICH) has been working to blend the approval process for new pharmaceutical drugs from Europe, the United States, and Japan, into one set of standards. This would reduce development costs, reduce the time to get drugs to market, and thereby assure greater profits. If the rush to "harmonise" to the lowest of existing standards leads to compromises in safety standards, there is good reason to be concerned.

Harmonisation of pharmaceutical regulation has important implications for public health, not just for the pharmaceutical marketplace. If public health were the priority, an International Conference on Harmonisation would differ substantially from the current ICH process. For a start, national governments and the WHO would be voting members, and the international and regional industry associations would be observers. Currently ICH operates in the opposite manner—it is *chaired* by the international brand-name industry association (IFPMA). The harmonisation should be reformulated into an open, accountable, and democratic process.

While not a voting member, Health Canada has adopted the vast majority of ICH guidelines through regulatory change.[1] There was no public debate, in Parliament or more widely, about Canada's adoption of ICH guidelines. Yet they will have a direct impact on the safety standards used by Health Canada when it approves new medicine and, unless proposed ICH standards for clinical trials are changed, a potentially negative impact on women's health.

Women and ICH

ICH proposals completely ignore the need for special research guidelines for women. Women use more medicines than men and are vulnerable in different ways. Women have also been disproportionately affected by some of the major drug disasters in the past that could have been prevented through better regulations, such as DES (diethylstilbestrol).[2] And women are still disproportionately affected: eight of the ten prescription drugs withdrawn for safety reasons from the US market between 1997 and 2001 affected more women than men.[3]

A key requirement of any new medication is that it must be effective and safe in treating the condition for which it was designed *and* for all of the populations that will be using it. The ICH created detailed guidelines for companies on ensuring ethnic representation, geriatric representation, and pediatric standards.[4] It is therefore imperative that:

- The ICH creates a Working Group on Women, using U.S. and Canadian guidelines as a starting point.
- ICH member companies be mandated to enroll women in *all* clinical trials of drugs that will be used by women, in numbers sufficient to be able to separately assess drug effectiveness, safety, side effects, and dosage levels for women as compared to men. Government regulators, such as Health Canada, should ensure that adequate monitoring and enforcement of these guidelines take place.

A "Special" Population

Women have historically been underrepresented in drug research trials for fear that if they are, or become pregnant, the drug could cause birth defects in the child to be born. It is now recognized that women of childbearing age need not be excluded from research as long as they are using effective birth control methods. Enough women should be involved in all stages of drug development so that safety and efficacy can be analyzed separately for them. Results from male-only studies cannot be generalized for many reasons, including the following:

Enough women should be involved in all stages of drug development so that safety and efficacy can be analyzed separately for them.

- On average, women are smaller than men. Most serious side effects are thought to be dose related. When women take dosages designed only for men they are possibly getting a higher dose than may be safe. There is no mechanism in place to ensure that such trials include separate analyses in women to see if the drug works differently, so that appropriate dosage can be determined.
- Some drugs have adverse effects that women are known to be biologically more prone to than men, including cardiac effects like QT interval prolongation (abnormal cardiac rhythm).[5]
- Several drugs are known to be metabolized at different rates for women than men or are eliminated from the body in different ways. This can also affect the dosage women should be prescribed.
- On average, women use different combinations of medications than men; hence drug interactions that might occur in women will not be picked up if they are not analyzed separately.
- While women of childbearing age are now more routinely included in clinical trials, not enough are included in order to separately analyze the data.

To read about the wide range of public health concerns related to ICH and a detailed list of recommendations to protect public safety in relation to the ICH proposals, see the brochure, *Who Benefits? International Harmonisation of the Regulation of New Pharmaceutical Drugs* (in French and English), and the article, *International Harmonisation of Pharmaceuticals: Key Issues of Concern for Public Health,* at www.whp-apsf.ca.

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PUBLIC HEALTH vs. PROFIT

Communicating about Environmental Risks and Infant Feeding

Penny Van Esterik, Professor, Department of Anthropology, York University, World Alliance for Breastfeeding Action (WABA), National Network on Environments and Women's Health

Breastfeeding as a media subject is both sexy and emotional. Sometimes the media extols the many, well-documented benefits of breastfeeding. But on the subject of environmental toxins in mother's milk, newspapers and television frequently sensationalize the degree of threat. "Babies in Poison Peril from Breastfeeding", "Scientists Find Deadly Toxins in Mothers' Milk" are typical headlines on the subject.[1] Media reports seldom stress that it is not mothers who are poisoning their babies, but chemical companies and identifiable industrial processes. Rarely cited are studies that indicate the levels of toxins found in breastmilk are falling.[2]

Media reports can have a direct impact on policy and on breastfeeding women. An article in the *Bangladesh Observer* stated, "With new information on the hazards of breastfeeding and the link between dioxins and cancer, it may be necessary to review our position on advocating breastmilk".[3] Bangladesh has an infant mortality rate of 69.68 per 1000 live births;[4] any decline in breastfeeding would significantly increase that rate. Reports about toxins in the breastmilk of Inuit women in Canada left some women frightened and desperate. One mother decided to stop nursing in an effort to protect her new baby; after several weeks of being bottle-fed a mixture of water and Coffee-mate, the baby was hospitalized.[5]

Hazards in infant formula, which is marketed as the best alternative to breastmilk, is rarely publicized by the media. Clinical evidence provided by medical research shows there is cause to be concerned about, as one example among many, the dangers of nitrates in water used to reconstitute infant formula.[6] In the face of commercial interests that benefit from casting doubts on breastfeeding, it is essential that there be accurate reporting about the risks and benefits of all forms of infant feeding.

In order to determine what the accumulating, and often contradictory, evidence concerning breastfeeding and environmental toxins tells us and to consider what messages should be communicated to women about this evidence, I reviewed the medical, social science, and advocacy literature on the topic. The scientific research indicates that, first of all, everyone, not only breastfeeding women, carries a body burden of toxic chemicals. All babies, not just breastfed ones, are exposed pre-and post-natally. Breastmilk is often used by medical researchers as a gauge of human exposure to environmental toxins not because it is "more toxic" than

Media reports seldom stress that it is not mothers who are poisoning their babies, but chemical companies and identifiable industrial processes.

other substances such as urine or blood, but because breastmilk fat is more easily and cheaply obtained for testing[7] and because the "fat soluble pollutants are likely to be found in higher concentrations in milk than in blood or urine".[8]

Some of the most exhaustive studies of toxic contaminants in breastmilk have been done in the Netherlands where the population has been exposed to the heaviest industrial pollution in Europe.[9] The work of Rogan and associates in North Carolina represents a second cluster of exhaustive studies.[10] PCBs, dioxins, pesticides, phthalates, and heavy metals have been found in samples of breastmilk from some women. The long-term effects of contamination are not yet known, but the evidence suggests that no adverse effects on growth or occurrences of illnesses in the first year of life are attributable to the presence of these chemicals in human milk, except in the case of extreme levels of contamination as in accidental industrial spills. One of the most authoritative reference texts on this subject, *Chemical Compounds in Human Milk*, concludes: "Virtually all national and international expert committees have hitherto concluded—on the basis of available information—that the benefits of breastfeeding outweigh the possible risks from contaminants present in human milk at normal levels."[11]

How can accurate information about risks and infant feeding be communicated to the media and to breastfeeding women? By placing the issue in a broader environmental health context. The following principles might serve as guidelines for coalitions of breastfeeding advocates, health advocates, and environmentalists who want to work together to send clear and accurate messages to the public:

- Acknowledge what is known about contaminants in breastmilk.
- Stress prenatal exposure as contributing to the body burden of all babies, not just breastfed babies.
- Identify the source of the pollution (chemical industries), not the source of evidence (breastmilk).

- Stress the risks associated with artificial breastmilk substitutes and the risks of not breastfeeding.
- Draw attention to alternatives to toxic products not alternatives to breastmilk.

Women have the right to know the milk they produce is as pure as it can be. Only by reducing environmental pollution can this right become a reality.

Penny Van Esterik's book, *Risks, Rights and Regulation: Communicating about Risks and Infant Feeding* (2002) is available from the World Alliance for Breastfeeding Action (e-mail: secre@waba.po.my) and on-line as a discussion paper from:

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LESSONS FROM THE PAST – ONGOING RISKS

Beyond DES – Hormones in the Environment

This article is based on excerpts from Hormonal Pollution Alert: Protecting our Long-Term Health, Protecting the Environment *by Ellen Reynolds, DES Action Canada*

DES (diethylstilbestrol) exposure is often viewed as a health issue unique to those exposed to the drug and an issue that is no longer relevant. This is far from the truth. DES exposure and long-term exposure to any synthetic hormone concerns a much broader population than those directly exposed to DES. In fact, the entire population is exposed to synthetic hormones like DES, from sources such as chemical pollution, medicines, plastics, paints, and pesticides on food. Many synthetic chemicals in the environment are harmful to our health. Some are so-called "hormone disrupters" and mimic synthetic estrogens like DES.

There has been strong evidence about the effects of these substances, but many questions are still unanswered.[1] By serving as a "human-effect model", the DES-exposed population demonstrates the potential effects of long-term exposure to synthetic hormones on the entire population and suggests answers to many of these questions.

Animal studies linking DES and estrogen exposure to cancer date as far back as 1963. [2] The prevailing belief at the time, however, was that the effects found in animal studies did not translate to the human population. When cancer was eventually found in DES daughters, it was clear that the animal studies did in fact predict these cancerous changes much earlier.

It had also been mistakenly accepted that the placental barrier was a protective guard for the embryo and fetus and that only radiation had the power to pass that barrier. Both DES and thalidomide proved that theory wrong. In both cases, the timing of the drug was a crucial factor. Some women took only very low doses (two or three tablets) of thalidomide during weeks five to eight of pregnancy, a crucial development period for the arms and legs of the fetus. Most of their babies were born with limb deformities or without limbs. Many women who were prescribed DES only took a small quantity of the drug during a critical period of sexual development of the fetus. Children exposed *in utero* before the 10th week of pregnancy experienced structural deformities and a greater risk of developing vaginal cancer.

The DES tragedy demonstrates a unique lesson about long-term effects. The delayed and often hidden effects of DES exposure clearly illustrate the need for comprehensive testing of the long-term safety and effectiveness of prescription drugs. These effects also point to links between disease and

The delayed and often hidden effects of DES exposure clearly illustrate the need for comprehensive testing of the long-term safety and effectiveness of prescription drugs.

DES Action Canada

DES Action Canada is the only consumer organization in the country alerting the Canadian public and health professionals to the on-going risks related to the drug DES (diethylstilbestrol). DES, a synthetic estrogen, was prescribed to millions of pregnant women in Canada and the U.S. between 1941 and 1971 in the mistaken belief that it would help prevent miscarriage.

Long-term effects of DES exposure were first observed in the children of the women prescribed DES. Many sons and daughters exposed *in utero* have developed numerous health problems including malformed reproductive organs, fertility problems, problems with pregnancy, endometriosis, immune system disorders, and cancer. The mothers who were prescribed DES have an increased risk of developing breast cancer.

DES Action Canada was founded in Montreal in 1982 by Harriet Simand and her mother Shirley. A few months earlier Harriet had been diagnosed with clear cell adenocarcinoma linked to the drug DES that had been prescribed to her mother during pregnancy twenty years earlier. By 2002, DES Action Canada had 11 volunteer chapters across Canada.

The mission of DES Action Canada is to identify, educate, provide support to, and advocate for the people exposed to DES, and to work towards the prevention of similar public health problems, particularly in the field of reproductive health care.

Women and Health Protection was spawned by DES Action Canada through the Centres of Excellence for Women's Health program in 1997.

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long-term exposure to environmental synthetic hormones or endocrine disrupters.

Endocrine Disrupters: What are They?

Each year over 400 million tons of 70,000 different chemicals are produced and released into our environment worldwide.[3] Some of these agricultural and industrial chemicals and certain heavy metals are referred to as "endocrine disrupters" or "hormone disrupters" because they interfere with the delicate balance of the endocrine system (the system that regulates hormones).

Endocrine disrupters include many of the chemicals used in the production of plastics, pesticides, pulp, and paper. They are also produced as unintentional chemical by-products of industrial processes or waste incineration from landfill sites or toxic waste dumps. Endocrine disrupters are found in the air, water, and soil, and they accumulate in the fat tissue of wildlife and humans.

From the list of known endocrine disrupters, the top 12, so-called Persistent Organic Pollutants, or POPs, have been identified by United Nations Environmental Programme as extremely toxic and are currently targeted for reduction and elimination internationally.[4] Very low levels of these toxic substances can affect drastic changes that may lead to cancer, problems with the nervous system, the immune system, and the reproductive system, especially for the fetus and young children. POPs "bio-accumulate" and magnify in concentration up the food chain.

Endocrine disrupters interfere with the endocrine system in various ways, generally resulting in either an increase or decrease in the normal hormonal levels in the bloodstream. They may mimic or block hormones such as estrogen (female hormone) or androgen (male hormone) or interfere in other ways, including affecting the thyroid function. The end result is a mechanism that scrambles chemical messages (hormones) resulting in a variety of adverse health effects.

Generally, the effects on wildlife include: the feminization of males, masculinization of females, deformities of reproductive

organs, enlarged thyroid, birth defects, behavioural changes, weakened immune systems, and increased vulnerability to disease, including cancer. The most pronounced effects on wildlife are found in top predators due to bio-accumulation which is, of course, of great concern to humans as we are at the top of the food chain.

Studying these effects on humans is made extremely difficult in an environment that is saturated with the natural hormones of our bodies and synthetic hormones from chemicals and medicines. Another problem is that there is no "control group" or unexposed group to use as a reference—everyone on the planet is exposed to endocrine disrupters. For this reason, it is extremely unlikely that scientists will ever be able to scientifically prove the exact connection between endocrine disrupters in the environment and the specific effects on humans.

Some endocrine disrupters will cause an adverse effect in extremely low doses while higher doses will have no apparent

The Over-Prescription of Benzodiazepines

Renée A. Cormier

The over-prescription of benzodiazepines (tranquillizers) was first identified as a critical health care issue among Canadian women through the pioneering work of Ruth Cooperstock and colleagues, who reported that women are prescribed benzodiazepines at twice the rate of men (Cooperstock, 1976; Cooperstock & Hill, 1982; Cooperstock & Lennard, 1979). Guidelines specify that benzodiazepines should only be prescribed for seven days to four weeks, but there is evidence that individuals are regularly prescribed the drugs for periods far in excess of ten days, and in some cases, for as long as twenty years (Ashton, 2002). Prolonged use of benzodiazepines results directly in a variety of health problems such as increased risk of hip and femur fractures and impairments in memory and general intelligence (Ashton, 2002; www.benzo.org.uk).

The Benzodiazepine Research Advisory Group, affilated with the British Columbia Centre of Excellence for Women's Health, collaborated with stakeholder groups and undertook an extensive literature review. Key gaps in knowledge, research, and programs were found that must be addressed in order to protect the health of Canadian women and men from the negative effects of long-term benzodiazepine use. These are:

- **benzodiazepine usage patterns in various sub-populations of Canadians;**
- **health consequences of long-term use;**
- **prescription patterns by health service providers;**
- **prevention and education efforts targeted at key stakeholder groups;**
- **a comprehensive intervention strategy directed at benzodiazepine-dependent individuals.**

A bibliography of the literature related to benzodiazepine use and overuse, including the sources mentioned here, is available at www.bccewh.bc.ca.

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effect. The reason for this is timing: by disrupting natural hormonal timing at critical moments of development, endocrine disrupters can potentially change the course of development and have drastic, life-long consequences.

Certain hormone-related cancers have been linked to endocrine disrupters: prostate cancer (a 126% increase between 1973 and 1991 in the U.S.), breast cancer (1 in 9 women will develop breast cancer in her lifetime in North America), uterine cancer, ovarian cancer, and testicular cancer.[5] Also, cases of non-Hodgkin's lymphoma, a cancer that can originate anywhere in the body, has almost tripled since the 1950s and is found in areas of high herbicide use, affecting farmers, herbicide applicators, and golf course supervisors.[6]

Endocrine disrupters are the suspected cause of many problems related to fertility and the female reproductive system. Problems such as infertility, ectopic pregnancy, miscarriage, endometriosis, and lactation failure have all been linked to exposure to endocrine disrupters in animal studies. Endometriosis, a reproductive disease characterized by the growth of endometrial cells outside the uterus, has also been linked to endocrine disrupters.

The Precautionary Principle

The precautionary principle is an international concept that has been developed over many years as an approach to environmental issues and human health. The concept is based on the idea of a "better safe than sorry" approach to the way society cares for the environment and human health and has been embraced in numerous international declarations and agreements.

For people who have been exposed to DES, many questions remain about further exposure to synthetic estrogens or other synthetic hormones. For example, it is unknown how DES daughters react to oral or injectable contraceptives, fertility drugs, or hormone replacement therapy. For this reason, specialists suggest it may be safer to avoid further exposure to synthetic hormones when possible. Based on the experience of the DES-exposed population and the harmful effects of this government-approved drug, drug regulators should be applying the precautionary principle to long-term drug testing and safety, and governments should be applying it to the regulation of synthetic hormones in the environment.

Hormonal Pollution Alert: Protecting our Long-Term Health, Protecting the Environment first appeared in the form of a public education resource kit containing 10 fact sheets. It also appeared, in part, in the *DES Action Newsletter*, Issue 65, Spring 2001. Both documents are available from DES Action Canada, 5890 Monkland Avenue, Suite 203, Montreal, Quebec H4A 1G2, toll-free 1-800-482-1-DES, http://www.web.net/~desact.

NOTES

1. For an elaboration of this issue, see Colborn T, Dumanoski D, Myers JP. *Our Stolen Future*. New York: Dutton, 1996.
2. Dunn T, Green, A. Cysts of the epididymis, cancer of the cervix, granular cell myoblastoma, and other lesions after estrogen injection in newborn mice. *Journal of the National Cancer Institute* 1963;31:425-38.
3. United Nations Environmental Programme (UNEP), 1998.
4. UNEP, 1998.
5. Epstein SS. *The Politics of Cancer Revisited*. USA: East Ridge Press, 1998.
6. Steingraber S. *Living Downstream: An Ecologist Looks at Cancer and the Environment*. New York: Addison-Wesley, 1997; 52-53.