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Are Women More Vulnerable to Environmental Pollution?

Maureen E. Butter

Science Shop for Biology, Science and Society Group, University of Groningen,
P.O. Box 72 9700 AB Groningen, Netherlands
Fax: 0031503635, E-mail: M.E.Butter@rug.nl

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ABSTRACT Environmental health of women is compounded by biological factors and social circumstances like poverty, gender inequality and gender invisibility. This paper explores biological differences with respect to chemical hazards. Biological differences abound on all levels of organization, from the molecular level to the brain. Gender differences in toxicity have been reported for many substances. Most research into chronic toxicity and gender has been directed at reproductive health and reproductive cancers. Reproductive effects on offspring quality have been reported for both sexes and can have multigenerational effects. Uptake, transport, metabolism, storage, and excretion account for many differences in internal exposure. There are also inherent differences in toxic response. Many differences are influenced by sex steroids. There is a general dearth of data, in particular with regard to environmental contaminants. Because of a general synergy between toxic substances and infectious diseases, environmental pollution aggravates the burden of disease in a more than disproportional way. This is not accounted for in the health statistics. Regulation of female immune system differs from men. Most autoimmune disorders show strong gender disparity, and for some autoimmune diseases environmental or occupational exposures are known risk factors. A good strategy would be to systematically research important pollutants like pesticides and blacklisted substances for gender differences, or explore diseases with strong gender disparity for environmental risk factors. It is recommended to give equal priority to chemical hazards and infectious diseases and address them simultaneously. Given the long-term and often multigenerational effects on population health, it is paramount to specifically include women.

INTRODUCTION

Environmental degradation exerts an increasing toll in social costs and non-renewable natural resources in the developing world. Moreover, environmental burdens in terms of health outcomes are very unevenly distributed, affecting the poor disproportionally. A large part of the world's population is exposed to both traditional environmental hazards from infectious diseases and modern hazards from pollution and depletion of resources. This double burden of risks has a strong gender dimension, affecting women differently from men.

Sims and Butter (2000, 2002) have sketched a comprehensive framework to address the gender dimension in the field of health and environment. There are many processes affecting access to and quality of resources differently for both sexes, resulting in different hazards and exposures. Although complex and interconnected, there are three broad categories to consider when addressing gender, health and environment: biological differences, the gender division of labor, differences in power, status and visibility. This paper will focus on biological differences in vulnerability to chemical pollution.

ENVIRONMENTAL POLLUTION AND HEALTH

Most environmental standards are based on animal data only. These data are extrapolated to humans, with a safety factor of 100 to allow for differences between humans and test animals and for differences within the human population at large (Manahan, 1994). Human data, as far as they go, are derived from occupational exposures and environmental incidents, generally involving high exposures. There are little data on chronic exposure to low doses and we know even less of the effect of the daily cocktail of hazardous substances to which a large part of the population is exposed (Ivanov et al., 2004). Many studies referring to gender differences merely report anecdotic material about different outcomes by gender, but these may reflect differences in exposure rather than differences in vulnerability. Apart from cancer, studies into chronic toxicity tend to focus on reproductive failure or hazards to the developing fetus and infant. Adverse effects on pregnancy outcomes and fetal health have been reported for many environmental and occupational chemicals: pesticides, dioxins and PCBs, heavy metals and plasticizers with little or no attention to other female reproductive

disorders like endometriosis, sexual health or menstrual disorders (Kauppinen et al., 2003). Yet, the reproductive health effects of POPs (persistent organic pollutants) and other endocrine disruptors are disquieting enough in themselves. POPs may cause moderate to severe congenital defects, impairing health over multiple generations. Other endocrine disruptors may change offspring health in very minute concentrations (Tamburlini et al., 2002, Damstra et al., 2002, Baccarelli et al., 2002, Rier and Foster, 2002, Sinaii et al., 2002, Silbergeld and Flaws, 2002). Male sexual and reproductive health was disregarded for a long time, but receives a lot of attention of late. Recently Anway et al. (2005) found that the pesticides vinclozolin and methoxychlor reduced male fertility in rats up to the fourth generation. Women are more vulnerable to cadmium and lead. Cadmium accumulates in the renal area and in bone, causing renal dysfunction and osteoporosis. The EU's Scientific Committee on Occupational Exposure Limits (SCOEL) recommended lower occupational standards for women for lead, because of its fetal toxicity. Already in 1985, women's greater vulnerability to disturbance of haem synthesis from lead was known. Yet, the SCOEL experts noted that there were no gender data on neurobehavioral effects: studies involved all male groups and that there was a dearth of data on male reproductive toxicity (European Commission, 2002). From pharmacological data, it appears that women generally suffer more and more severe adverse effects from pharmaceuticals (Drici and Clement, 2001, Rademaker (2001).

Rinn et al (2004) surveyed the male and female expression patterns of 13,977 mouse genes in hypothalamus, kidney, liver and reproductive tissue. Substantial differences were found in kidney, liver and reproductive tissue. These genes were involved in drug and steroid metabolism, in osmotic regulation and other cell functions (Rinn et al., 2004). Physiological and anatomical gender differences abound on all organization levels, from the molecular basis to brain functions (Van der Pol-Meijer and Butter, 2003). This would imply that, toxicologically speaking, men and women are different species. Inter-species differences in vulnerability are sometimes negligible, but occasionally quite large.

DIFFERENCES IN INTERNAL EXPOSURE

Toxic substances enter the body either by oral, respiratory or dermal route. On their way into the body and bloodstream, they may cause local damage. But once in the blood, they are transported to organs and tissues, their sites of action, sites of metabolism, sites of storage, and sites of excretion. The kidney is the major site of excretion, but it can only handle water-soluble substances. Anatomical and physiological differences between the sexes may result in differences in internal exposure. Men have larger average lean body mass and higher water content, resulting in higher distribution volume for water-soluble substances, thus more dilution. A modifying factor is that xenobiotics in blood readily bind to plasma proteins, thus making them less bio-available. Plasma protein is a temporary storage site, protecting against acute effects. The xenobiotics lose the bond when encountering a site to which they have greater affinity (Hodgson and Levi, 1994). Higher bioavailability of some drugs has been reported for women, one explanation being down regulation of plasma proteins by sex steroids (Morris et al., 2003).

Substances that are difficult to metabolize are stored, mostly in liver, bone or adipose tissue, depending on fat-solubility (Hodgson and Levi, 1994). A number of toxic substances have a long half-life in the body. Many persistent pollutants accumulate in fat and nervous tissue, which is also rich in lipids. Weight loss may mobilize these body burdens (Imbeault et al., 2002, Charlier et al., 2002). Many POPs have endocrine disrupting and immunotoxic properties, for example dioxin has been associated with endometriosis and other autoimmune diseases (Baccarelli et al., 2002, Rier and Foster, 2002, Sinaii et al., 2002). Filtration capacity of the kidneys is larger, leading to faster excretion of water-soluble substances via the bladder, assuming they are not actively taken up again.

Women have larger relative fat mass, thus larger distribution volume for fat-soluble substances. Most environmental chemicals are highly lipophilic. Many of them pass readily through the skin (dermal route).This route is important for formal and informal occupational exposures, as well as exposures from cleaning agents, cosmetics and other products applied to the skin. Although the skin forms a formidable barrier to many substances, small fat-soluble compounds readily pass the skin. Also, skin damage and degreasing by detergents diminish the skin's barrier function (Hodgson and Levi,

1994). This is important, because prevalence of skin diseases is larger in women, and also because women's exposure often involves wet agents (Kauppinen et al., 2003). Fat-soluble substances also bind to plasma proteins.

Eventually, most fat-soluble substances end up in the liver, the largest organ for biotransformation and eventual detoxification. Liver enzymes metabolize xenobiotics, making them more water-soluble during the process. Often, the metabolites and intermediate products are more toxic than the mother compounds. In Phase 1, which is dominated by the well known P450 cytochromes, generally referred to as CYP, a polar group is added, making is accessible to Phase 2 reactions, in which water-solubility is further increased, enabling the kidney to excrete it. There are important sex-linked differences in the CYP enzymes and activity, which are partly regulated by the sex steroids. Some substances are more rapidly metabolized in female liver cells, but since the end products of Phase 1 are often more toxic than the original substance, it may result in higher internal exposure in women (Donovan, 2005, Harris et al., 1995, Hodgson and Levi, 1994, Gandhi et al., 2004, Silbergeld and Flaws, 2002, Schwartz, 2003). Schwartz (2003) remarks that most studies don't take the size difference into account when evaluating gender differences. Controlled for lean body mass, male livers metabolize most substances faster. Only CYP3A4 substances are faster cleared by women, but the difference is not a substantial one. Sex steroids modulate CYP activity, but there are innate differences too (Schwartz, 2003).

Phase II also shows gender differentiation. Moreover, pregnancy, menopause and menstrual phase influence Phase II activity (Hodgson and Levi, 1994). Substances entering via the oral route have to pass the gastrointestinal tract. Little is known about gender differences in transport over intestinal epithelium (Morris et al., 2003). But since gastric emptying in women is slower, toxic substances will stay longer in the intestinal tract. The intestinal flora has more time to metabolize it, often rendering it more toxic than the original product (Donovan, 2005). The respiratory route leads through the lungs. Gas exchange takes place through the cells forming the wall of the alveoli. Uptake via the lung is a lot faster and a lot more efficient than the oral route. Aerosols are tiny droplets or particles suspended in air. The smaller the particles the deeper they penetrate in the airways. Depending on the substances attached to the particles or solved in the droplets, they may cause local effects in the alveoli which make the lung more permeable. Other substances are retained by the lung, and irritants and allergens cause local inflammation and may lead to acute or chronic lung damage (Hodgson and Levi, 1994). Gender differences have been reported for transport as well as for local effects (Plopper et al., 2001, Morris et al., 2003, Donovan, 2005).

Water-soluble compounds are readily excreted. Xenobiotics bound to plasma proteins may be actively excreted (Hodgson and Levi, 1994). In general renal excretion is faster in men than in women (Morris et al., 2003, Schwartz, 2003). Some substances accumulate in the kidney. It may cause problems there, if it is nephrotoxic or carcinogenic. Cadmium retention in the kidney is higher in women. Renal Cd retention is modulated by the sex steroids: it has been demonstrated that the female sex steroid estradiol slows down Cd excretion in male rats (Nishiyama et al., 1988, Vahter et al., 2001). Ochratoxin, a nephrotoxic and carcinogenic mycotoxin shows more retention in male rats (Zepnik et al., 2003). Large molecules are also excreted via liver and bile. Molecules solved in bile are released into the intestine and partly re-absorbed. Excretion via bile is a passive process, therefore rather inefficient. Volatile substances can also be excreted via the lungs. Like excretion via the bile, this is a passive process. An important excretion route for women is linked to reproduction: persistent substances are transferred to the fetus and are released with breast milk. There are some other elimination routes: substances can show up in sweat, skin oil, hair and nails (Hodgson and Levi, 1994).

DIFFERENCES IN VULNERABILITY

As far as gender-related health effects from environmental exposures are not caused by differences in external or internal exposure, they have to do with inherent differences in vulnerability. Since many environmental contaminants exercise their action by binding to the body's receptor, sexual differences in receptor density or sensitivity and any modulation by the sex hormones may result in sexual differences in vulnerability. A great many processes in the body are mediated by sex steroids. Receptors for estrogens and androgens are all over the body,

modulating toxic response in a sex-specific way. Endocrine disruptors, lead and mercury affect offspring differently for boys and girls. Breast cancer and other reproductive cancers have been associated with various environmental pollutants. PCBs and dioxins have been associated with endometriosis and autoimmune disorders. Toxic response to cadmium differs in a sex-specific way. Recent studies show, that women's risk to lung cancer and cardiovascular disorders associated with smoking and environmental tobacco smoke are higher than men's (Keitt et al., 2004, Silbergeld and Flaws, 2002, Tamburlini et al., 2002, Sharrett et al., 2004).

A good starting point for research would be to examine the gender differences in susceptibility to important pollutants like pesticides and blacklisted substances like heavy metals and POPs. A recent finding of importance in this respect is that plasma levels of pesticides in residents of a Punjab village were up to 650 higher than in U.S. residents (Mathur et al., 2005). Another point of departure might be diseases with a strong gender disparity. The immune system is of prime importance. First, because it is a major part of the body's defenses against xenobiotics. Large molecules evoke an immune response from B and T cells as well as natural killer cells. Second, there are major interactions between toxic substances and infectious diseases. It has been demonstrated that simultaneous exposure to xenobiotics and common viruses lowers the resistance to infection and conversely, increases uptake, accumulation and toxic action of xenobiotics (Bacarelli et al., 2002, Funseth, 1999, Funseth et al., 2000, 2002a, 2002b, Glynn et al., 1998, Kaltreider et al., 2001). Third, because of women's greater susceptibility for autoimmune disorders, many of which have a known association with environmental pollution. The female immune system must accommodate for pregnancy. It would not do to have an immune reaction to the embryo or fetus. In pregnancy, the immune response is reduced and it is likewise reduced in the luteal phase of menstruation (Fessler, 2003, Shinoda et al., 2003, Souza et al., 2001). Given the different organization of the immune system, gender differences in immune system-related diseases are to be expected. Autoimmune diseases are far more prevalent in women. This is not the case for all autoimmune diseases: in some there is no gender difference and others, in particular kidney autoimmune disorders, have larger prevalence in men (Beeson, 1994). Sex steroids play a role in autoimmune disease pathogenesis (Ahmed et al., 1999, Offner, 2004, Palaszynski et al., 2003, Beagley and Gockel, 2003, Olsen and Kovacs, 2001). Fisher et al (2005) found that TCDD (a dioxin) in a mouse model selectively eliminates T cells, but saves autoreactive T cells. This effect was more prominent in males. Autoimmune diseases also have been related to PCBs, asbestos, pesticides, solvents and other xenobiotics (Kita and Gershwin, 2004, Cooper and Parks, 2004, Cooper et al., 2004, Pfau et al., 2005).

CONCLUSION

Above I have reviewed some mechanisms, that might lead to higher vulnerability in women for some substances and under certain conditions. Men's larger distribution volume for water-soluble toxics may be compensated for in the oral route by women's slower gastrointestinal passage, and in the respiratory route by men's larger lung volume. The dermal route is quite impermeable for water-soluble toxics, except where it concerns wet exposure and damaged skin. These form a specific risk for women. Men's faster clearance of water-soluble metabolites also results in comparatively higher internal exposures for women. Persistent lipophilic substances stored in adipose tissue may cause more problems to women during periods of fat mobilization, that is during pregnancy and dieting. The same goes for substances stored in bone, as women have periods of large bone turnover, i.e. pregnancy and menopause. Substances that form a substrate for CYP3A4 in Phase I transformation may be more rapidly metabolized by women. If Phase II is not faster than in men, this would result in higher internal exposures for the presumably more toxic metabolites. Most problematic are those substances, to which women have higher receptor affinity as well as higher internal exposure. Women's immune system seems more vulnerable than men's. Evaluation of toxic substances in a gender-sensitive way should take these differences into account, apart from the reproductive differences.

POLICY IMPLICATIONS

From the above, it is clear that chemical occupational and environmental hazards is a

gender issue, deserving full attention of gender researchers as well as environmental experts. Yet, neither chemical hazards nor women's health receives too much political attention in many developing countries. Even taken from a health perspective only, the environmental burden of disease may seem less significant than traditional problems of infectious disease and malnutrition. But given the significant synergies between chemical pollution, infectious diseases and malnutrition, it is certain that the health impact of chemicals is heavily underestimated. Chemical pollution can impair population health over many generations, and it should be addressed simultaneously with infectious diseases and malnutrition. A first priority is to obtain adequate information about environmental pollution and to establish and enforce environmental legislation to reduce chemical pollution, especially of blacklisted substances. As for the gender dimension, in order to reduce population health impacts, it is important to identify occupational and non-occupational sources of exposure as well as body burdens in all subpopulations and to identify and protect vulnerable groups. Because of women's general invisibility, overlooking the gender dimension may have important long-term population health consequences.

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