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NeuroToxicology



Neurotoxic exposures and effects: Gender and sex matter! Hänninen Lecture 2011

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ABSTRACT

Although males and females differ both biologically and in their social and power relations throughout their life span, research in environmental and occupational neurotoxicology often ignore sex and/or gender as a characteristic that requires in-depth consideration. The neurotoxicology literature continues to confuse the terms sex (biological attributes) and gender (socially constructed roles and behavior) and the words are still used interchangeably. Throughout the lifespan, sex and gender are in interaction and both may play a role in influencing exposure and effect. Studies that have examined both males and females, provide evidence for sex differences in toxicokinetics and responses to neurotoxic assault as well as gender differences in exposure patterns, biomarkers of exposure, neurobehavioral performance and social consequences. Integrating sex and gender considerations into research in neurotoxicology would not only provide us with a better understanding of the mechanisms and pathways that lead to toxic assault, but also provide a means to improve preventive intervention strategies.

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Although it may seem a pleonasm to say that males and females differ both biologically and in their social and power relations throughout their life cycle, studies in neurotoxicology often ignore sex and/or gender as a characteristic that requires consideration. In a thought-provoking article entitled “*Same sex, no sex and unaware sex in neurotoxicology*”, Weiss (2011) points out that sex differences are disregarded in much of neurotoxicology research, noting that the large majority of behavioral experiments are performed using male animals, while *in vitro* studies wholly ignore sex. Favoring males in the choice of subjects is not limited to neurotoxicology, Beery and Zucker (2011) estimated male bias in animal research as the ratio of the percentage of women in the total population presenting with a disease with regards to the percentage of females in rat and mouse models of that disease. Neurosciences are at the top of their list of male bias in biomedical research.

But what about studies of neurobehavioral performance in human populations exposed to neurotoxic substances? Contrary to animal or cell studies, where researchers select specific strains for study, in human epidemiology research, the choice lies in the selection of groups occupationally or environmentally exposed to potentially harmful chemicals or persons with or without a specific disease. Is there a male predominance in these population-based studies? And if so, what are the consequences on our understanding of the associations between exposure and effect and does this influence policies and intervention strategies to reduce exposure

and mitigate effects? Do gender and sex considerations matter in neurotoxicology research with human populations? This question formed the basis of my Hänninen Lecture on gender and sex considerations in neurotoxic exposures and effects. As I read and organized the material, my answer evolved from yes, sex and gender matter, to my final version where sex and gender matter is followed by an exclamation point. Here, I share some of the thoughts and ideas that lead to the exclamation point.

1. Sex or gender?

In the early nineties the term ‘gender’ entered the neurotoxicological literature and there was much confusion over whether to use ‘sex’ or ‘gender’ to differentiate males and females. For a while, gender became the ‘politically correct’ term and many researchers used and still use the words gender and sex interchangeably. Although there are many definitions for sex and gender, sex generally refers to biological attributes and gender to socially constructed roles and behavior. In most studies of nonhuman animals, sex is the appropriate term to differentiate males and females.

The Committee on Understanding the Biology of Sex and Gender Differences of the United States’ Institute of Medicine (IOM) (Wizemann and Pardue, 2001) defines gender as: “A person’s self-representation as male or female, or how that person is responded to by social institutions based on the individual’s gender presentation. Gender is rooted in biology and shaped by environment and experience”, while others, like the Canadian Institutes for Health Research, include the notion of power: “the array of socially constructed roles and relationships, personality traits, attitudes, behaviors, values, relative power, and influence that society ascribes

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to women and men. Gender is often referred to in binary terms (i.e., feminine or masculine); however, there are many locations on the gender continuum.” (CIHR, Institute for Gender and Health Strategic Plan 2009–2012). In an on-line course developed by the United States’ National Institutes of Health on the science of gender and sex in human health (NIH <http://sexandgendercourse.od.nih.gov/courses.aspx>), the authors put forward that “Imprecise use of the terms “sex” and “gender” has serious implications for future biomedical research, clinical practice, and treatment. Without a clear distinction between sex and gender, the nature of related health outcomes and differences in health status will be inadequately understood and addressed.”

Indeed, sex and gender represent different aspects of maleness and femaleness, but, similar to the nature/nurture dichotomy, one continually influences the other throughout the lifespan. Fig. 1 schematizes these interactions at key periods in life. For example, adolescent girls and boys may be involved in different types of activities, which translate into different exposure profiles; the effects of these exposures on neurological and psychological functions may be dissimilar due to metabolic and hormonal differences, which in turn manifest as gendered behavior patterns. In the report of the IOM Committee on Understanding the Biology of Sex and Gender Differences, the authors discuss some of the difficulties in separating out social and biological contributions to health problems (Wizemann and Pardue, 2001). In neurotoxicology, while there is much overlap in male and female exposures and neurobehavioral responses, considering sex and gender differences may be important to better understand the mechanisms and pathways that underlie the complex relations between exposure and effect.

2. Male predominance

In occupational health, there is a historic and still persistent belief that hazards are characteristic of many male-dominated jobs, while women’s working conditions are less harmful. Consequently, women workers’ health problems are not necessarily linked to their work environment and are often viewed as resulting from their greater susceptibility as the “weaker sex”. Concern about this image of women and work was voiced in the early 20th century by Alice Hamilton (1869–1970), the mother of modern occupational medicine, who wrote about lead poisoning in both men and women industrial workers (Hamilton, 1919). In her biography, Hamilton (1943) noted that cases of lead poisoning and elevated blood lead levels, observed proportionally more

frequently among women industrial workers compared to men, was often attributed to sex differences in lead susceptibility. She put forward that the higher prevalence of lead poisoning in women workers was rather a reflection of job differences since women were in poorer paid jobs with higher lead exposures. Almost a hundred years later, London et al. (2002) describe a similar situation with regard to pesticide exposure in South Africa, where enhanced surveillance revealed that, contrary to the official statistics, women had a higher prevalence of pesticide poisonings compared to men, reflecting higher exposures in women, who did more seasonal work with high exposures and were likewise more exposed in the home. The authors underline that women’s pesticide-related health problems were often misdiagnosed because of the dominant belief that women were not exposed ‘like men’ to pesticides.

Messing aptly calls occupational health research ‘One-eyed Science’ (Messing, 1998). She notes that while men’s working conditions are well documented, there is comparatively little research on women’s work, leading to a vicious circle of ignorance: if a situation is not recognized as dangerous to health, there is minimal interest in studying it and if it is not studied, it is not recognized as dangerous. Several authors have pointed out the dearth of studies on women’s occupational health (Hunt, 1979; Stellman, 1994, 1999; Messing, 1998; Messing and Mager Stellman, 2006), but few have examined this specifically in studies of neurotoxic exposures.

I began by examining my own publications on neurotoxic effects of occupational exposures. Of the 27 articles, published between 1985 and 2008, in over half (55%), men constitute the entire study group, in 22% both men and women are included, in 19%, the study group is referred to as “workers” and the sex of participants is not mentioned in the article; only one focused solely on women. Were my studies representative? I then explored the men and women’s distribution in recent studies of occupational exposure to organic solvents, based on a Medline search, using the words: (Neurobehavior* OR Neuropsychologic*) AND solvent* AND (occupation* OR worker* OR workplace OR profession*). The search was limited to humans, the past ten years (from May, 2011) and excluded meta-analyses and clinical reports. A total of 34 papers were identified. Ten of these studies (29.4%) included only men, ten studies (29.4%) comprised both sexes and three (8.8%) only women. In nine studies (26.4%), participants were described as workers and sex was not provided. These findings are similar to those reported by Messing and Mager Stellman (2006), who analyzed how gender was taken into

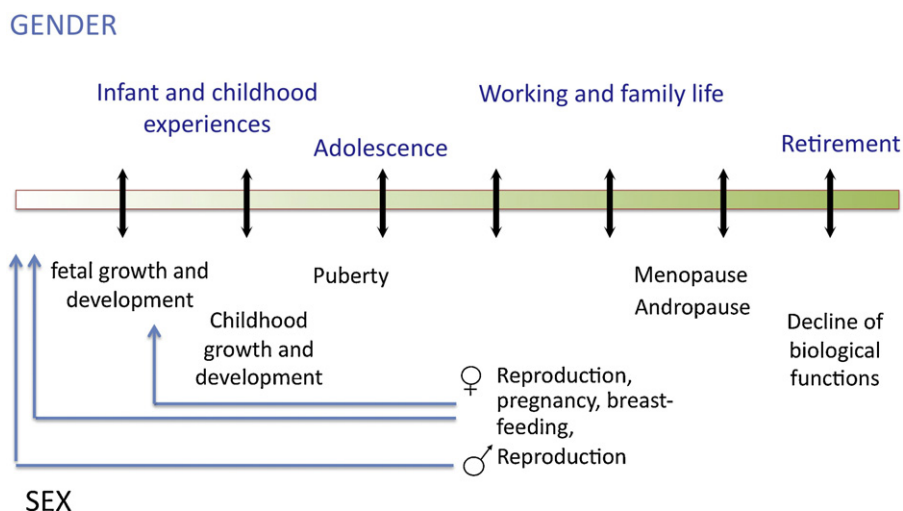


Fig. 1. Schematic representation the interactions of gender (socially constructed roles and behavior) and sex (biological attributes) throughout the lifespan.

account in 11 studies of mercury exposure in chloralkali plants as part of a systematic search of occupational health studies for the period from 1996 to 2002. Shih et al. (2007) identified and reviewed 21 studies carried out between 1996 and 2006 on neurobehavioral effects of lead exposure in adults in relation to biomarkers of current (blood) and cumulative (bone) exposure. Men made up 100% of the study group in the majority of the 15 occupational studies (73%). It is noteworthy that Helena Hänninen's pioneering study (Hänninen et al., 1991) on the effects of neurotoxic exposure in twins where one, but not the other, was exposed to organic solvents, is notable not only for its findings on solvent neurotoxicity but also because an equal number of men and women workers were included in the study.

Surprisingly, despite the large body of literature on the effects of gestational exposure on neonates and children's neurodevelopment with respect to environmental exposures, there are relatively few studies on women workers' exposure to toxic chemicals and their children's capacities. In a systematic search targeting epidemiological studies on occupational exposure to industrial chemicals and subsequent neurodevelopment, Julvez and Grandjean (2009) identified only 15 studies, which focused on working women; they were exposed to organic solvents or pesticides.

Although there are probably more jobs occupied by men with chemical exposures compared to jobs carried out by women, the distribution of men and women in studies on neurotoxicity of occupational exposures does not necessarily reflect the distribution of exposure. In a random telephone survey on men's and women's working conditions, Eng et al. (2011) indicate 57% of men and 34% of women report workplace exposure to dust and/or chemical factors. Women's underrepresentation in occupational health studies reflects not only the belief that women's exposure at work may be less than men's but also that women are often excluded from studies in order to maintain a homogeneous sample, particularly when there are proportionally fewer women than men in a workplace (Messing, 1998; Gochfeld, 2007). Another factor that may explain the imbalance is that exposure studies are often carried out in major industries, where workers are predominantly men, while women's exposure may be concentrated in poorer paying jobs, with less bargaining power. It is interesting to note that in Helena Hänninen's twin study, none of the exposed men, but half of the exposed women, were classified as unskilled or semi-skilled laborers (Hänninen et al., 1991).

In studies of environmental exposure both sexes are typically included, but usually with little concern for possible differences in exposure profiles or outcomes (Vahter et al., 2007a; Gochfeld, 2007). Participants' sex is provided, but for the most part, it serves as a co-variable entered into multiple regression models to account for possible sex or gender related differences with little indication about what these differences mean or represent.

3. Sex/gender differences

Over the past years, several authors have examined sex disparities in toxicokinetics (Clewel et al., 2002; Vahter et al., 2002, 2006, 2007a,b; Gochfeld, 2007; Lindberg et al., 2008; Berglund et al., 2011; Madison et al., 2011). In 2007, the Human Health Working Group of the Scientific Group on Methodologies for the Evaluation of Chemicals (SGOMSEC)-16 published their findings on issues pertaining to sex and gender in toxicology. The group provide an overview of sex and gender dissimilarities in exposure, kinetics, target organ response and gene expression (Vahter et al., 2007a) and put forward that biological and/or socially constructed differences exist from the gamete to old age and should be examined in research and risk assessment (Gochfeld, 2007; Vahter et al., 2007a,b). Among their recommendations, the authors include the need for future toxicological

studies to investigate differential responses resulting from sex dimorphism in the Central Nervous System structure and function (Vahter et al., 2007a).

In neurotoxicology, animal studies, which have examined male and female offspring separately, report sex differences in behavioral responses to gestational exposure to several chemicals, including lead (Leasure et al., 2008; Cory-Slechta et al., 2004, 2010; Cory-Slechta, 2005); methyl mercury (Rossi et al., 1997; Giménez-Llort et al., 2001), polychlorinated biphenyls (Schantz et al., 1995; Kremer et al., 1999; Widholm et al., 2001; Geller et al., 2001; Boix et al., 2011) pesticides (Dam et al., 2000; Levin et al., 2001, 2002), organic surfactants (Onishchenko et al., 2011). In a recent study of manganese-exposed adult mice, long-lasting differences in neuronal morphology were observed in females, but not in males, in the absence of differences in manganese accumulation in the brain (Madison et al., 2011).

3.1. Patterns of exposure

In humans, both gender and sex influence exposure and effects throughout the lifespan. From childhood, girls and boys come into contact differently with their surroundings. For example, a study of farm workers' children showed that boys had more frequent contacts with their environment while girls had contact with fewer objects but longer durations (Beamera et al., 2008). The authors aptly point out that "Understanding how frequency and duration contribute to dermal and non-dietary ingestion exposure could increase understanding of the potential difference in exposure between the genders". A study of children living around a dumpsite reported that boys roam in contaminated areas more than girls (Stegmann and Hewner, 2000). Larson and Verma (1999) reviewed a large number of international studies on children's and adolescents' work, play and development and noted, not surprisingly, that boys carry out more outdoor chores, while girls carry out more indoor chores.

In adulthood, men and women are likewise involved in different work and household activities, which translate into different exposures not only in the workplace, but also for household products, including domestic use of pesticides. Hobbies, another potential source of exposure, may likewise differ by gender. In addition, beauty aids, whose use is gendered, are another potential source of exposure. For example, skin whiteners, which can contain inorganic mercury, are primarily used by women; high blood and urinary mercury have been reported among users in several countries (Chan, 2011).

3.2. Biomarkers of exposure

While exposure profiles may be gendered, biological differences can influence chemical absorption, metabolism and excretion; both are reflected in biomarkers of exposure (Vahter et al., 2007a). Vahter et al. (2007b) provide an insightful review of studies on sex differences in the disposition and toxicity of metals; the authors further note the importance of age-related events, such as child-bearing and menopause. Lindberg et al. (2008) showed higher arsenic methylation efficiency in women of child-bearing age, compared to men, which the authors suggest supports an influence of sex hormones. In a study of serum PCB concentrations in adolescents living in polluted and non-polluted areas (Nawrot et al., 2002), boys presented fifty percent higher PCB levels compared to girls, but these sex-related differences in serum PCB concentration disappeared after allowing for calculated body fat content. The authors discuss the role of changes in body fat with respect to PCB concentrations throughout the lifespan, particularly for women, since breast-feeding and weight loss are known to affect PCB body burden (Nawrot et al., 2002).

A further example is from the Canadian Health Measures Survey: males present higher volume-based urinary BPA concentrations compared to females, but lower creatinine-standardized urinary concentrations of BPA (Bushnik et al., 2010). The reversal in sex difference was attributed to urinary creatinine concentrations. The authors conclude that these differences in urinary BPA concentrations may reflect differences in exposure and/or pharmacokinetic factors, the relevance of which is not currently known. Barr et al. (2005) who analyzed urinary creatinine data from the United States' Third National Health and Nutrition Examination Survey (NHANES) data, show that age, sex, race/ethnicity, body mass index, and fat-free mass are significant predictors of urinary creatinine and propose that the analyte concentration, unadjusted for creatinine be included in multiple regression analyses, with urinary creatinine added as a separate variable.

3.3. Neurobehavioral performance and conduct

Some studies of neurobehavioral performance have examined males and females separately. Lead (Pb) is the most studied neurotoxic agent in children. Table 1 presents results of cognitive function and behavior from birth cohort studies, which reported Pb-related deficits in boys and girls separately. The Cincinnati birth cohort studies (Dietrich et al., 1987; Ris et al., 2004) indicate that Pb-associated cognitive deficits were more frequent in boys compared to girls (Table 1), consistent with the study carried out by Bellinger et al. (1990), where at 5 years of age, girls had recovered from prenatal Pb exposure deficits in cognitive performance observed at 2 years of age, but not boys. In the Flemish Environment and Health Study, Vermeir et al. (2005) reported cognitive decrease associated with current Pb blood concentrations for 17-year-old boys and not for girls, but there was no information on prenatal Pb exposure. At low prenatal exposures, Jedrychowski et al. (2009) observed cognitive loss in boys at 3 years of age in relation to fetal exposure, but not in girls. On the other hand, several studies have reported Pb-associated cognitive deficits in girls, but not in boys (Rabinowitz et al., 1991; Baghurst et al., 1992; Tong et al., 2000).

Behavioral difficulties have been associated with Pb exposure in both boys and girls (Table 1), but not necessarily for the same types of behavior. Leviton et al. (1993) examined 8-year-old children's behavior in school. Teacher assessments at 8-years-old revealed that for girls, elevated umbilical cord blood Pb was associated with dependent and non-persistent behavior, and an inflexible and inappropriate approach to learning tasks, while in boys, with cognitive difficulty for both simple directions and sequences of directions. In these girls, elevated deciduous tooth dentin lead content was associated with reading and spelling difficulties, performing learning tasks, and with "not functioning as well as peers", but no association with elevated dentin lead concentration

was observed in boys. On the other hand, Dietrich et al. (2001) observed no differences in reported delinquent behavior for adolescent girls and boys from the Cincinnati Birth Cohort Study, and the *gender* × *Pb* interaction term was not significant. Wright et al. (2008) reported on arrest rates from this same cohort for young adults of 19 and 24 years of age. Although the *p*-values for the interaction term *gender* × *Pb* were consistently above 0.05, the attributable risk for young men was considerably higher than for young women; the attributable risk for 6-year blood lead rate was 0.85 arrests/year (95% CI: 0.48–1.47) for men and 0.18 (95% CI: 0.09–0.33) for women.

Differences between boys and girls have also been reported for other toxic substances. Poorer motor performance was observed in relation to prenatal methyl mercury MeHg in 7-year-old boys, while other functions were similarly affected in both sexes (Grandjean et al., 1998). Prenatal exposure to phthalates has been associated with greater risk for behavioral disorders in boys between the ages of 4 and 9 years (Engel et al., 2010). Boys likewise presented greater risk for early childhood symptoms of ADHD in relation to mothers' exposure to organophosphate pesticides (Marks et al., 2010), but IQ deficits were similar in boys and girls from this cohort (Bouchard et al., 2011a). However, in an analysis of data from the NHANES, Bouchard et al. (2010) observed similar associations for boys and girls between metabolites of organophosphate pesticides and ADHD cases, defined as meeting DISC-IV criteria or taking ADHD medication, with the adjusted OR for girls: 2.09 (95% CI: 1.39–3.15) and for boys: 1.60 (95% CI: 1.09–2.36). Guo et al. (1995) reported that among Taiwanese school-age children whose mothers when pregnant had been exposed to PCBs through contaminated cooking oil, boys showed a greater effect compared to girls on the Raven's Standard Progressive Matrix Test. On the other hand, Jacobson and Jacobson (2002) noted no clear pattern of differential gender vulnerability: stronger inverse associations with prenatal PCBs were observed for 11-year-old boys on full scale IQ, while deficits in reading word comprehension were stronger for girls. Furthermore, for the WISC-R, an inverse relation was observed for perceptual organization for boys, while for girls it was with mental rotation processing speed.

In two cross-sectional studies of school children exposed to elevated manganese in air and water (Riojas-Rodríguez et al., 2010; Bouchard et al., 2011b), the inverse relations between manganese exposure and full IQ were stronger in girls than boys; other studies on manganese exposure in children did not present their results separately for boys and girls. In adults, although women present higher blood manganese compared to men (Baldwin et al., 1999), men present more deficits than women (Mergler et al., 1999). Rothlein et al. (2006) have likewise reported gender differences in response to pesticide exposure among Hispanic agricultural workers, with women doing more poorly compared to men on some measures.

Table 1

Reported gender differences in neurobehavioral studies of children in relation to lead (Pb) exposure. When indicated cognitive (Cog) or behavioral (Beh) effects were reported in one sex but not the other.

Biomarker and level of exposure	<i>n</i>	Age	Boys	Girls	Country	Reference
Maternal blood mean 8 µg/dL	302	6 month	Cog		USA	Dietrich et al., 1987
Dentine mean 4.0 µg/g	402	6 year	Cog		England	Pocock et al. (1987)
Med cord blood 6.2 µg/dL	192	8 year	Beh	Beh	USA	Leviton et al. (1990)
Med dentine 2.8 µg/g	192	8 year		Beh	USA	Leviton et al. (1993)
Dentine mean 4.7 µg/g	515	6.7 year ± 0.4		Cog	Taiwan	Rabinowitz et al. (1991)
Cord blood 8.7 µg/dL	495	6–7 years		Cog	Australia	Baghurst et al. (1992)
Life-time exposure	322	11–13 years	Beh	Beh	Australia	Burns et al. (1999)
Life time exposure	325	11–13 years		Cog	Australia	Tong et al. (2000)
Pre and post natal blood Pb	195	15–17 years		Beh	USA	Dietrich et al. (2001)
Pre and post natal blood Pb	195	15–17 years	Cog		USA	Ris et al. (2004)
Current ~2 µg/dL (GM)	200	17 years	Cog		Belgium	Vermeir et al. (2005)
Med cord blood 1.21 µg/dL	457	3 years	Cog		Poland	Jedrychowski et al. (2009)

3.4. Social consequences

Gendered behavioral manifestations of intoxication may differ throughout the lifespan. Landrigan et al. (2002) estimated the loss of earnings associated with early life Pb-related loss of IQ. Because of higher revenues, the estimated lifetime loss for men is higher than women, but because women are in the lower income range, the impact on poverty status may be higher. Increased risk behaviors, delinquency and criminal arrests, which have been associated with several contaminants (Dietrich et al., 2001; Wright et al., 2008; Aschengrau et al., 2011), may also present differently in males and females.

The social manifestations of neurotoxic damage affect not only the exposed persons, but also their families. In a study of men occupationally exposed to neurotoxic chemicals, we observed a positive relation the workers' exposure level, their psychological symptoms and wives' report of marital conflict (Julien et al., 2000). The life cycle of malnutrition presented in the World Health Organization's document on indicators of environmental health (World Health Organization, 2002) can also be applied to toxic exposures. Fig. 2 is an adapted version highlighting life cycle effects of a young woman with elevated toxic exposures who gives birth to a daughter. During pregnancy, the mothers' neurotoxic substances are passed on to her child. The infant receives further toxics along with the nutrients in maternal milk. The infant girl plays in a dusty contaminated environment, putting objects and dirty hands into her mouth. Exposed *in utero* and during early childhood, as a school child, she is listless, performs poorly and has behavioral problems, leading to early school dropout. For teenage girls, this may lead to early pregnancy, and the cycle continues, compounding the effects of the toxic exposure. Early pregnancy may be an outcome to examine with respect to toxic exposures.

4. Sex and gender matter!

There is consensus on male over-representation in both animal and human studies in neurotoxicology, leading to a "one-eyed" understanding of the relationship between toxic exposures and neuro-outcomes. From a methodological point of view, the predominance of male-based models influences our thinking on relevant exposures and biomarkers of exposures, sensitive outcomes and social consequences. Nonetheless, the evolution of

gender roles in society is reflected in science and over the past years and in keeping with the overall changes in the biomedical and population research, there is a growing interest in integrating gender and sex considerations in neurotoxicology. To do so, however, requires us to broaden our thinking and develop a new paradigm for sex and gender-sensitive research.

5. Suggestions for sex- and gender-sensitive research in neurotoxicology

5.1. Research question

Messing et al. (2003) put forward that taking gender and sex into account begins with the research question. Does the research question apply to both males and females? If one is proposing to study one sex or the other, the research question should state this. Were the studies that support the research question performed with only sex or with both? If so, what are the implications for the research? Is gender taken into account in the research question?

5.2. Study design

There is a wide range of designs and here I do not attempt to cover all, but present some questions to consider. If the study includes exposure assessment of both genders, are the activities and habits of both adequately considered? If it is a workplace study, does job title adequately reflect job task and exposure? Is the sample size sufficient to demonstrate possible differences? Are there sex and/or gender-related factors that could influence the relation between exposure and biomarkers of exposure? If so, what are the strategies to consider these differences? Are the outcome measurements relevant for males and females? Could gender differences in social or computer-based activities influence the outcomes? Have the individual outcome measures been validated for males and females? For studies that include the social consequences of exposure, are they equally relevant for both genders?

5.3. Analyses

In neurobehavioral research, most studies include sex as a co-variable in multiple regression analyses. While these analyses

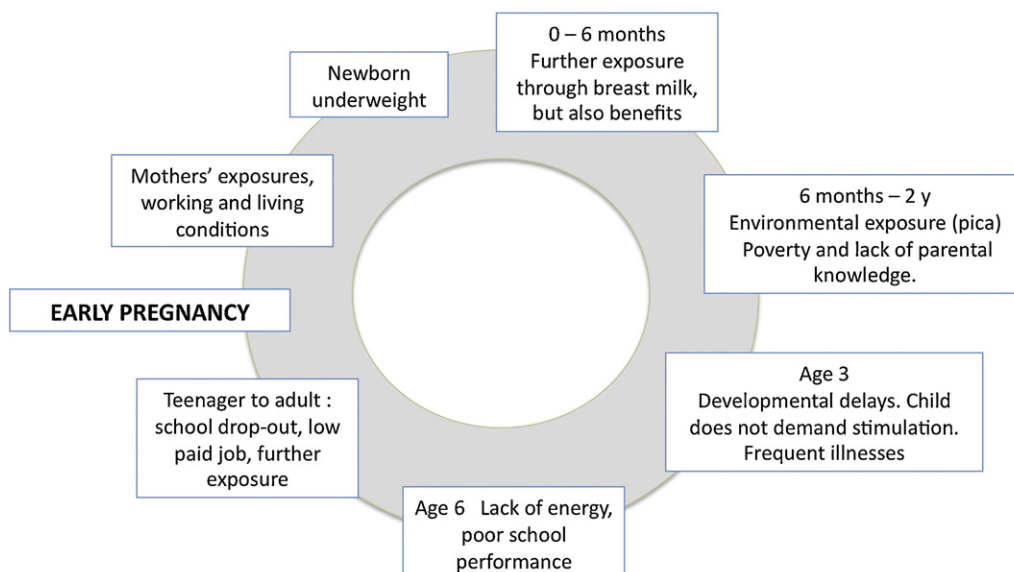


Fig. 2. Exposure and early pregnancy: adapted from 'Using Indicators to Measure Progress on Environmental Health, WHO (2002)'.

provide valuable information on the overall associations between exposure parameters and effects, they say little about possible sex and gender differences. Studies that have examined males and females separately, usually include gender as a covariable, test for a gender–exposure interaction and then perform separate analyses when the sex–exposure interaction term was significant. In other areas of occupational and environmental health, gender-stratified analyses have shown that the relevant co-variables may be different for males and female (Messing et al., 2009; Silverstein et al., 2009; Abdelouahab et al., 2008). Some studies have shown notable differences in findings when using gender adjustment or stratifying techniques and suggest stratifying from the beginning of data analysis to better understand the relation between exposure and effect in males and females (Silverstein et al., 2009; Messing et al., 2009). Härenstam (2009) proposes that traditional epidemiologic techniques could be complemented with contextual and comprehensive approaches, such as multilevel or clustering analyses. Some of these techniques have been discussed for neurobehavioral studies with respect to race/ethnicity and socio-economic status (Bellinger et al., 1989; Bellinger, 2008).

It is noteworthy that in neurotoxicological studies, which have examined males and females separately, no clear pattern has emerged, even with prenatal lead exposure, the most studied exposure situation. Several reasons may explain these inconsistencies, including exposure differences during childhood, measured outcomes, social influences and statistical analyses. A worthy undertaking would be to perform a meta-analysis with the wealth of data that exists on neurobehavioral effects of prenatal exposures to lead and other neurotoxic substances. Different analytical strategies, such as those mentioned above, could be used in this and other endeavors to understand male and female differences.

5.4. Data interpretation

Understanding sex and gender differences is not only useful for elucidating mechanistic bases of neurotoxicological changes and the pathways from exposure to effects, but may as well provide new insights into prevention strategies. In the 2005 Hänninen Lecture, Anger (2007) invited participants to expand the focus of neurobehavioral research to include prevention. Indeed, mitigation takes on a new dimension in light of current knowledge that many environmental contaminants continue to circulate in the environment and will do so for many years to come, despite improved regulations and reduction of exposure at the source. Furthermore, since prenatal exposures have long-lasting effects, health and education interventions directed to reducing the gravity of effects should be considered. Identifying gender and/or sex related factors that influence the pathways between exposure and effects will be useful in designing effective measures to reduce exposures and long-term harm.

5.5. Publications

Scientific journals could play a more pro-active role in ensuring that the terms 'sex' and 'gender' be appropriately applied or defined differently. Editors and reviewers could ensure that the title adequately reflects whether the study was performed with one sex or both sexes, and that if the study is performed with just one, there is an explanation of this choice and the limits in generalizing the results to the entire population are stated.

5.6. Granting agencies

While granting agencies have played a very positive role in putting forward the need and importance of sex and gender considerations in health research, the funds to carry out this work are

not necessarily forth-coming. Because of the increased complexity and additional time required in carrying out gender/sex analyses, a financial incentive for studies that include a gender/sex analysis may help to implement these ideas. The application forms for the Canadian Institutes for Health Research ask whether sex and gender are taken into account in the proposal, but I have seen no study that analyzes the responses as such or in relation to funding.

6. Conclusions

Gender and sex analyses in neurotoxicology research adds a new dimension that can increase our knowledge on the underlying mechanisms and pathways, as well as provide new directions for prevention. The exclamation point in "sex and gender matter!" became imperative as I examined the evolution of my own work in occupational and environmental neurotoxicology and the body of literature. A new paradigm that would include sex and gender analyses requires us to ask different questions. Let's take up the challenge.

Conflict of interest

No conflicting interests.

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