Editorial

Sex differences in susceptibility to toxic industrial chemicals

In today's political world one frequently hears of a gender gap arising from the significant differences men and women display in their preferences for certain candidates for elected office or in their stands on certain issues. While the political gender gap is a relatively newly recognised and highly debated phenomenon other differences between the sexes have long been recognised, including the well established fact that women in the United States outlive men by about 7.5 years. What are the causes of this so called ultimate gender gap? Several theories have been proposed to try to explain this difference in longevity, including genetic factors,1-4 higher oestrogen levels affording women differential protection from cardiovascular disease,5 higher proportions of the male population in type A behaviour patterns,6-11 more reckless behaviour in men resulting in deaths from traumatic causes such as fatal accidents and suicides, and differential smoking activity.12-18

It is widely accepted that a substantial (although difficult to define precisely) proportion of chronic diseases in the population is associated and possibly caused by environmental agents. Indeed, one often sees figures suggesting that 60-90% of human cancers are related to environmental factors, depending on how broadly one chooses to define the term "environment." While usually not discussed as broadly, similar estimates of the impact of environmental agents on the occurrence of non-cancerous, chronic diseases may also be as high as the cancer estimates.

If one assumes that environmental exposure may play an important part in the occurrence of serious chronic diseases in the United States then what percentage of the difference between men and women in longevity is due to the differences simply in exposure? For example, since men smoke more than women, they run greater risks of lung cancer. On the other hand, could there possibly be differences in the inherent susceptibility to toxic agents between the sexes; and could this be a factor affecting the ultimate gender gap?

The prime research and regulatory emphasis in the fields of environmental and occupational health has focused on the identification of toxic agents and their effects. There has been considerably less interest in the development of an understanding of host factors which may modify the occurrence of environmentally induced disease. Nevertheless, it is widely accepted that age, genetic background, and nutritional status may appreciably affect the occurrence of environmentally induced disease in animal models and man.

Over the past several years I have made a comprehensive search of published reports for the occurrence of sex related responses to pollutant and drug related toxic effects. This effort culminated in the publication of my book entitled Toxic susceptibility: male/female differences (Wiley-Interscience, 1985) which considers the question of whether, and to what extent, men and women differ in their response to toxic substances. That sex related differences exist in response to these agents has been suspected since the early 1900s.19 20 The need to assess whether the sexes differ in response to toxic substances, however, is of exceptional current importance, given the rapid influx of women into traditionally male orientated occupations. In fact, most workplace health standards tend to be based on criteria derived from the assessment of how men have responded in the historical past to pollutants.21 Consequently, it is not uncommon to have women workers "protected" by health standards designed to protect men. In addition, federal laws have emerged that indicate that the workplace must be safe for pregnant women without regard to the developing embryo/fetus which is legally not considered to have constitutional rights. If the law protects pregnant women then to what extent does pregnancy affect susceptibility to toxic agents? At present, environmental and occupational health standards have not given consideration to the issue of whether pregnant women differ in susceptibility to toxic agents as compared with non-pregnant women and men.

Just briefly, Toxic susceptibility: male/female differences establishes that sex related differences in response to toxic substances occur in a sizeable number of species and for a large number of toxic agents. More specifically, sex related differences have been found to occur in chickens, mice, rats, hamsters, gerbils, guinea pigs, rabbits, dogs, and man. The number
of toxic substances for which sex related differences have been found to occur is extensive and approaches nearly 200.

Whereas the range of species in which sex related differences to toxic agents have been studied is extensive, the published research on sex differences has principally focused on the responses of the rat. Consequently, much of what is known about sex differences in response to toxic substances is based on the rat model. This is undoubtedly related to the fact that rats are traditionally used in a wide range of toxicity tests and naturally sex differences, if they exist, would very likely be observed. This would not be the case for other possible models with the exception of the mouse, since models such as the cat, dog, and monkey are studied only to a small extent compared with the rat. Thus the absence of sex differences in many less used species may not so much reflect non-existent sex related differences but an absence of evaluation of whether such differences exist. While all the above is true, it is also apparent that the rat more than any other species displays a striking series of sex related differences in the metabolism, detoxification, and biointoxication of toxic agents. In fact, if it were not for the basic reality of such sex differences in response to toxic agents in rats this field would not have evolved as quickly and as extensively as it has.

The examples of where sex related differences in human responses occur comprise a small percentage of the total cases of such differences. None the less, several dozen examples of sex related differences in response to either toxic agents or drug metabolism or both are listed in the table.

An important aspect of the findings is that neither sex emerges as truly, naturally superior—that is, more resistant. "Superiority" appears to depend on the substance in question. For example, while men appear more sensitive to cigarette smoking induced lung cancer and aflatoxin induced liver cancer, studies suggest that women are more susceptible to agents such as lead and lithium and retain benzene for a significantly longer time.

Regardless of the species concerned, it appears that the extent of the sex differences range from as low as 10% to as high as 1000% (or a 10-fold difference). The only exceptions to this range of sex differences are with respect to decalin, where the female rat is at least 100 times less sensitive than the male rat to renal toxicity, the 0-depropylation of coumarin in which the male rat displayed a 20:6-fold greater activity, and the acute toxicity of ethion in which the female rat displayed a 10:1-fold higher LD50 value. This type of information may play a potentially significant part in assessing the extent to which uncertainty factors may be used in the regulatory process.

To date, regulatory agencies have made some use of the knowledge of sex differences. For example, the recommended threshold limit values (TLVs) of the American Conference of Governmental Industrial Hygienists (ACGIH) (1980) reflect evidence of sex differences in response to toxic agents (aldrin, carbaryl, demeton, 1,3-dichloropropane, dyfonate, endosulfan, endrin, EPN, ethanolamine, ethion, and fensulthion) in the proposed exposure limits for some agents, such as endosulfan and ethion, but not all—for example, 1,3-dichloropropane. Nevertheless, the methodology by which knowledge of sex related responses was incorporated in the establishment of

### Examples of sex related differences in human responses to toxic or pharmacologic agents or both

<table>
<thead>
<tr>
<th>Substance</th>
<th>Response</th>
<th>Reference No</th>
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</thead>
<tbody>
<tr>
<td>Acetylaminofluorine</td>
<td>Preadolescent boys are at greater risk of developing AAF induced chromosomal aberrations (94.7% greater) and repair synthesis (34.3% greater) in fibroblasts</td>
<td>22</td>
</tr>
<tr>
<td>Aflatoxin</td>
<td>Men are 2:5 to 5 times more susceptible to developing aflatoxin induced liver cancer</td>
<td>23, 24</td>
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<tr>
<td>Benzene</td>
<td>Women display a 25% longer retention at 6 h</td>
<td>25</td>
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<tr>
<td>Dimethylbenzanthracene</td>
<td>Preadolescent boys display a 25–40% greater susceptibility to developing genotoxic alterations</td>
<td>22</td>
</tr>
<tr>
<td>Indocyanine green</td>
<td>Women display a significantly greater plasma fractional disappearance (by 13-9 to 19-7%) of indocyanine green than men</td>
<td>26</td>
</tr>
<tr>
<td>Lead</td>
<td>Women are 1:3 to 1:5 times more sensitive to lead induced changes in red cell biochemistry —eg, FEP and ALAU</td>
<td>27</td>
</tr>
<tr>
<td>Lithium</td>
<td>Women display a 5-fold greater risk of developing hypothyroid condition from lithium medication</td>
<td>28, 29</td>
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<tr>
<td>Lorazepam</td>
<td>The T1/2 for those aged 25–48 was 29-9% greater in men</td>
<td>30</td>
</tr>
<tr>
<td>Nortriptyline</td>
<td>Plasma levels of equal exposures showed a differential distribution with women showing 25-7% higher values</td>
<td>31</td>
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<tr>
<td>Oxazepam</td>
<td>The T1/2 for those aged 25–48 was 24-3% greater in women</td>
<td>32</td>
</tr>
<tr>
<td>Propoxyphene</td>
<td>Women have 20% of the volume of distribution of men</td>
<td>33</td>
</tr>
<tr>
<td>Rifampicin</td>
<td>Women absorb this antibiotic 10% more efficiently</td>
<td>34</td>
</tr>
<tr>
<td>Cigarette smoke</td>
<td>Men are about 2:5 times more likely to develop cigarette smoke induced lung cancer than women after adjustment for amount and duration of smoking, type of cigarette, amount of tars, technique of smoking, etc</td>
<td>15, 35</td>
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<tr>
<td>Testosterone</td>
<td>Women oxidise testosterone significantly faster than men</td>
<td>36</td>
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<tr>
<td>Trichloroethylene</td>
<td>Women excrete a higher percentage as acid while men excreted more as alcohol</td>
<td>37</td>
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</table>
TLVs was not presented. The United States Environmental Protection Agency’s ambient air and drinking water quality standards do not, as yet, seem to have taken possible sex related differences into account.

In conclusion, there is strong evidence for the existence of sex related differences to environmental and occupational toxic substances. These differences occur in a broad range of species including man and in response to a large number of agents. In addition, the magnitude of such differences is not trivial; it commonly exceeds severalfold and in limited cases exceeds an order of magnitude. That such differences exist may be of considerable public health importance as well as have numerous other social implications. The further documentation and assessment of these sex related differences in response to toxic substances will require the collaboration of experts in many areas for elucidation.

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References

7 Russek HL. Stress, tobacco and coronary disease in North American professional groups. JAMA 1965; 192:89-94.