Gender Neurotoxicity Chemicals Example

Gender Differences in Neurotoxicity Abstract Neurotoxicity is damage to the structure and/or function of the peripheral and central nervous systems. It is a common outcome of exposure to hundreds of environmental chemicals, which act via a wide range of mechanisms. Due to the fundamental importance of the nervous system to a fully functioning body, the neurotoxic effects of many chemicals have been well investigated. There is evidence from a number of studies of a difference in susceptibility to environmental neurotoxins between genders.

Males appear to be more vulnerable than females. There may be many reasons for this difference, a key one being the neuroprotective activities of the gonadal (sex) hormones, which differ between males and females. The female hormone, oestrogen, is thought to have greater protective activity, from a wide range of chemicals than the male hormone, testosterone. This report will examine the available evidence of a gender difference in susceptibility to environmental neurotoxins, and look into the actions of hormones within the nervous system as one of the main reasons for this difference. Introduction The nervous system (NS) is a fundamental component of a fully functioning human body.

Due to the immense importance of the NS, any damage that occurs to this system will have huge repercussions throughout the whole body. Unfortunately, the NS is extremely vulnerable, and neurons, with their unique shape, and long, thin extensions protruding from their cell bodies, are highly susceptible to degeneration, from ageing and from exogenous substances (1, 2). It has been observed that exposure to a range of different environmental chemicals can have adverse effects on the NS, resulting in degeneration of neurons, and leading to onset of various neurological diseases (2, 3). The developing NS in particular is extremely sensitive to the effects of such chemicals (2, 4). Prenatal, and early postnatal, exposure to environmental chemicals, such as lead and those in tobacco smoke, can affect the developmental process within the Central Nervous System (CNS). This can lead to slowed and incorrect development, and neurological problems in the early years of life (4). From both animal studies, and human case reports of inadvertent exposures, there is also evidence to suggest a difference between males and females in their susceptibilities to neurotoxicity of some environmental chemicals (5). There are a number of reasons why this may be, including differences in amounts and activities of metabolic enzymes, differences in rates of absorption between the sexes, different rates of clearance of exogenous substances from the body, and differences in exposure to neurotoxic chemicals; diet, hobbies, occupations, etc (6). However, a key reason may be the neuroprotection that is conferred by gonadal hormones, and their metabolites, within the NS (5). The aim of this report is to research evidence of sex differences in responses to environmental chemicals, and investigate hormonal influences as one of the reasons for this difference.

Neurotoxicity of Environmental Chemicals Neurotoxicity is a term used to describe damage to the structure and/or function of the peripheral NS (PNS) and CNS, brought about by exposure to particular exogenous substances (7, 8), which act via a range of mechanisms to induce cellular changes, and often cell death (7). Neurotoxicity can be seen in all ages of individuals exposed to hazardous chemicals, however, the developing NS is particularly vulnerable to their effects (2, 4, 7). Development of the NS involves a series of very specific steps, over a prolonged time period, each one occurring only when the previous is finished, and disruption to these events leads to incorrect development and neurological problems (4). The blood-brain barrier (BBB), which prevents many substances from passing to the brain, is not fully complete until several months of age, leaving the NS susceptible to damage (7). The entire NS is not fully mature until puberty (4). A great number of the reports

published concerning neurotoxic effects of chemicals have reported observations on child subjects. This is due to the fact that the developing NS is much more vulnerable, and so the neurotoxic effects may be more easily noticed. There are over 200 chemicals that have been confirmed as neurotoxic to humans (and other animals)as a result of exposure to them (3). A number of these chemicals are identified in Panel 1 (3), and can be divided into groups; metals, organic solvents, pesticides, and other neurotoxic chemicals. Panel 1. There are over 200 chemicals known to cause neurotoxicity in humans.

This list identifies some common ones. Adapted from (3). Chemicals in bold and red are those identified within this report. Different toxins have distinct mechanisms through which they influence the NS. This depends on dose, route and duration of exposure (9). Those chemicals which are most widespread in the environment, and those which cause the most drastic effects, have been extensively investigated, and many of the mechanisms causing neurotoxicity have been identified (9). Given the knowledge of these effects, it is important to investigate the possible neurotoxic influences of the large number of other chemicals prevalent in the environment. Mechanisms of neurotoxicity The main mechanisms encompassed by the afore-mentioned groups of substances include;

- induction of oxidative stress,
- alterations to neurotransmitter synthesis including inhibition of synaptic signalling,
- accumulation of the substance within mitochondria leading to dysfunction,
- alterations to the flow of ions across neuronal membranes,
- activation of second messengers to induce apoptosis or inhibit neurogenesis,
- disruption of DNA/RNA, affecting the differentiation and functioning of glial cells, to indirectly influence neuronal cells,
- alterations to membrane fluidity,

- abnormal expression of neurotrophic factors

(7, 10-20). There is a requirement for metals in many body processes, including within the NS, providing an additional mechanism by which exogenous metals can induce neurotoxicity (17). They can compete with essential metals for protein binding sites and influence cellular processes (17). For example, lead competes with zinc, which is known to have binding sites present in many important receptor channels, such as the N-methyl-D-aspartate (NMDA) receptor involved in glutamate signalling at the synapse. Lead can displace zinc, and therefore alter functioning of these channels, and so influence glutamatergic functions in the NS (13, 14, 17). A relatively recently proposed mechanism thought to induce neurotoxicity via environmental chemicals, is endocrine disruption. Endocrine disruption is believed to be a crucial mechanism of most neurotoxicants, including metals, solvents, pesticides, Polychlorinated Biphenyls (PCBs), Diethylstilbesterol (DES), etc (21-25). Endocrine disrupting chemicals act by mimicking, enhancing, or antagonising the effects of endogenous oestrogens and androgens (21, 22). Their actions can result in alterations to hormone synthesis and/or release, altered transport and clearance of hormones, altered binding of hormones to their receptors (by binding themselves, thereby either mimicking hormone response, or blocking hormonal activation (24)), or altering components of pathways following receptor activation (22). An example of an endocrine disrupting mechanism is one used by lead, which lowers blood levels of testosterone, thereby de-masculinising certain areas of the male brain, and PCBs, which both mimic and antagonise various oestrogenic functions, and disturb production of androgens (21). As hormones are known to have a role in the development of the CNS, including sexual differentiation (26), disruption to their activities may result in disruption to the development of some brain areas, and the possibility of feminisation or masculinisation of particular brain areas (21-25). The neuroprotective function of hormones (discussed later) may also be hindered due to the endocrine disrupting actions of certain chemicals, allowing for their other neurotoxic mechanisms to have greater damaging effects.

Neurotoxic investigations Carrying out investigations into the effects of neurotoxic chemicals is much more difficult in humans than it is in other animals, due to the greater difficulty in controlling the surrounding environment and its influences, and there are many potential variables that can have an effect on the overall

result, in particular exposure to other environmental chemicals, drugs, alcohol, tobacco, education, culture, etc (27-31). All the potential confounding factors must be taken into consideration in order to analyse the neurotoxic effects only of the chemical in question (32). Often, environmental chemicals induce delayed neurotoxicity, whereby a patient does not present with symptoms until well after exposure to the chemical has ended, providing another problem to investigators (4). There are many different symptoms that can present upon neurotoxicity; migraines or headaches, confusion, memory loss, Multiple Sclerosis (MS)-like symptoms, problems with sleep, balance and hearing, attention impairment and trouble concentrating, anxiety and depression (8). Alterations to cognitive function, motor function and behaviour are common outcomes of neurotoxicity, and are a useful assessment of the effects of exposure to chemicals (32, 33). There are a wide range of different tests commonly used to assess neurotoxicity to the PNS and CNS (4, 32, 33). Measurements of functions such as motor reflexes, insensitivity to pinpricks on the skin, or impairment of sensitivity to temperature and vibration, provide evidence of PNS toxicity (4, 32, 33). Other functional tests, including IQ (Intelligence Quotient) tests, memory tests, assessment of mood and personality, and behavioural questionnaires, are used to assess toxicity to the CNS (4, 32, 33). Damage to the Nervous System can also be established by use of various brain imaging techniques (e.g. Computed Tomography, Magnetic Resonance Imaging) (9). These are useful in observing physical alterations to brain size and appearance caused by brain tissue atrophy following neurotoxic exposure (9). It is also possible, using these images, to ascertain which regions of the brain are particularly affected (9, 33-35). Despite the large quantity of literature outlining investigations concerning exposure to different neurotoxic chemicals, there are relatively few publications available that have identified a difference in response between males and females. Differences between susceptibilities of a range of age groups, and groups with varying levels of exposure, have been acknowledged frequently (27, 36-38), however reports are rare in which results for men and women are assessed independently, therefore it is often difficult to determine any differences in susceptibility between the sexes. Many reports record numbers of each sex taking part in the study, and match controls accordingly, then proceed to analyse results as a whole (27, 28, 39-45). Others exclude female subjects altogether, rather than including analysis of female results, but separate from the male (29, 30, 46-51). This is often the case when the number of female subjects is small compared to men. However, the results could still be analysed, and any differences between them could be noted. Some fail to establish which sexes have been used at all (52-54).

Nevertheless, there is evidence from a number of reports, of a difference between genders in neurological functioning following exposure to neurotoxic chemicals. An extensive search using MEDLINE and EMBASE, of published studies and case reports into neurotoxicity of environmental chemicals, identified a number of studies which observed differences between males and females.

For the purpose of this report, only those chemicals with gender differences have been mentioned. Evidence of Gender Differences in neurological outcomes of exposure to Neurotoxic Chemicals Metals There are roughly 40 different metals that exist in the environment, some of which are essential for life to occur (e.g. copper, zinc, etc), others which aren't (e.g. mercury, lead, etc) (9). Exposure to metals in the environment has been known to cause adverse effects to both the adult and child human NS for many years (3). The neurotoxic effects of these metals are particularly well characterised, and have been well investigated.

Included in this report are three of the major neurotoxic metals, of which there has been much exposure to in the environment, and of which there has been some indication of a sex difference in susceptibility to neurotoxic effects; mercury, lead and manganese. These three metals have been more extensively investigated than others, and therefore sex differences observed should not be ruled out of others, and may also be noted if they are as well examined. Mercury Mercury can take various different forms, each of which has distinct effects on human systems (18). Methylmercury (e.g. contaminated seafood), ethylmercury (e.g. Thimerosol, a component of some vaccines), elemental Mercury (present in industrial vapours), and inorganic mercury compounds (e.g. skin lightening creams) (18). Of these forms, methylmercury has been acknowledged as having the greatest detrimental effect on the correct functioning of the human NS, and in particular, the developing nervous system of children (18). In adults, methylmercury is thought to damage specific brain regions, such as the visual cortex, and parts of the cerebellum, whereas in children, as the NS is not completely developed, the effects are thought to be more widespread (7). It has been observed in a number of studies that male children show greater impairments in NS functioning following exposure than female children. In certain neurological tests, which have an association with methylmercury exposure, namely those assessing finger tapping, tendon reflexes, and leg coordination ability, males achieve poorer results (8, 36, 37, 55-57). As the majority of studies reporting results

individually for male and female subjects are those carried out in children, the main sex differences reported here have been observed in children. However, similar results are noted in those adult investigations where males and females were analysed separately (27). McKeowyn-Eyssen et al. (1983), Cordier et al. (2002), Myers et al. (2003), Grandjean et al. (1998), and Marsh et al. (1987), all carried out numerous different tests on school children exposed to methylmercury at varying concentrations, pre- and post-natally.

Each of these groups identified that, for those tests which have been shown to be more affected by increasing methylmercury levels, including finger-tapping, abnormal muscle tone, tendon reflexes, and leg coordination, male children showed poorer results (19, 57-60). McKeowyn-Eyssen et al. (1983) carried out the same tests on adults, and found an indication of a similar sex difference, with men being more likely than women to develop neurological disorders, following increases in methylmercury levels (37). Davidson et al. (2000) found that male, but not female, responses in neurological tests increased with methylmercury exposure, which is the opposite of the expected results, however, numerous unexamined variables were identified, which could have had influences on the results of the tests (31). Holmes et al. (2003) identified a link between mercury exposure and autism in children. Higher mercury levels in the hair were found to be associated with milder autistic symptoms (61). Perhaps because those children with milder symptoms were more able to excrete the mercury through their hair, before too much damage occurred. There was a greater number of females showing milder autistic symptoms, and a greater number of males showing severe autistic symptoms (61). From the evidence put forward here, there is a definite implication of a greater susceptibility for males than females to the neurotoxic effects of methylmercury exposure. There is an increased risk of neurotoxicity for children of women with increased levels of mercury in the hair (61). Hair mercury levels in subjects themselves, following equal exposure between the sexes, has been observed on numerous occasions as being lower in males than females, when associated with neurological problems (37, 61, 62). It may be that females have a better ability to excrete mercury through the hair than males, so less is present in body tissues. Lead Lead has long been known as a neurotoxicant, and its widespread release into the environment over the years has resulted in many neurological problems, mainly linked to learning difficulties (17), that have been well studied and characterised (3). Lead toxicity is thought to occur mainly in the hippocampus, cerebellum, and prefrontal cerebral cortex and again, it is thought that children,

with their NS still developing, are at greatest risk to the neurotoxic insults of lead (7), so the majority of reports found here have been carried out in children.

The elimination of lead from many environmental sources, such as motor vehicle petrol, and paints, has seen a decline in the amount of toxic lead exposure (7). However, it is still a problem in many areas, for example those homes where lead paint has been used in decoration (17). There are a number of studies that have reported a difference in cognitive impairments between male and female children. Tests carried out on school children, in South America, the UK and USA (38, 63-66), all identify a larger correlation between lead levels in the blood and poor cognitive ability in males than in females, while Wasserman et al. (1998) state that mothers reported behavioural problems with male children exposed to lead, more often than with exposed female children (67). An assessment of behavioural problems associated with lead exposure in American children (68) and an assessment of intelligence of children following lead exposure in Port Pirie (69), identified no difference between males and females in the results of their tests, while an assessment of the capabilities of children in school, and association with lead exposure (70), along with another investigation of child IQ by Needleman et al. (71), observed results to suggest females were more susceptible to lead neurotoxicity than male subjects, as they appeared to have greater prevalence of learning difficulties associated with lead. So, there appears to be a significant amount of evidence implying a gender difference in neurotoxicity associated with lead exposure. The majority of reports imply an increased susceptibility for males; however it is important for groups to look at sex differences in future studies, in order to ascertain conclusive results. This evidence also provides a need for investigation of sex differences in effects of lead exposure in adults.

Manganese Manganese is another commonly used metal that can cause a toxic effect the NS upon exposure (20, 29, 40, 46, 47). There is a risk of manganese toxicity in various professions, in particular, welding (29, 46), but also through drinking or washing in water containing extraordinarily high levels of manganese (20, 40). There are a large number of reports confirming the neurotoxicity of manganese (20). Investigations have shown decreased intellectual ability in children over-exposed to manganese (40), and mood disturbances in men exposed occupationally (e.g. welders, factory workers.) (29, 40, 46, 47). In children, a report into an association between

hair manganese levels and prevalence of hyperactivity, found that while there was a higher amount of manganese present in girls than boys, no difference was found between the sexes in assessment of neurological behaviour tests (72). Perhaps female brains are better able to cope with a higher amount of manganese. In adults, Dietz et al. (2001) found that a relationship between levels of manganese exposure and its effect on the Globus Pallidus area of the brain was seen only in men. These investigators give the reason that female workers have lower blood concentrations of manganese, and have a lower cumulative exposure index (73). However, they do not state whether there was a difference in actual exposure between sexes. If the exposure levels were the same, this could be an indication of increased susceptibility to males. In another study, results of neurological tests following manganese exposure were poorer for men than for women (74). As the majority of studies on manganese actually exclude females from results, or do not give separate results for each sex, it is difficult to make any definite assumptions about gender differences in neurotoxicity susceptibility. Implications from the three studies above provide a suggestion of a sex differences in manganese toxicity, with a greater effect within males. However, in future studies, where possible, females should be included, and the results analysed separately, in order to establish conclusive evidence for sex differences in neurotoxicity to manganese. Solvents There is a vast array of solvents that are used in many different industries and work places, meaning daily exposure for many different workers, including hairdressers, laboratory workers, painters, dry cleaners, and carpet layers, among others (33, 75-78). Due to the composition of solvents, they are particularly dangerous to the tissues of the NS. They are lipophillic compounds, and therefore have strong affinity for tissues rich in lipids, including the brain (33, 79). It is thought that psychomotor performance is the most common deficit (51) of solvent exposure, and prolonged exposure can cause permanent damage (15). Other symptoms include anxiety, insomnia, irritability, memory loss, fatigue and seizures (15, 33, 75). Solvent substances most often consist of a mixture of different chemicals, which can affect different regions of the brain.

This can result in difficulties determining the toxic effects of a particular chemical (9). There have been many studies published that report clear association between solvent exposure and neurological deficits. Nelson et al. (1994) report that solvent exposure in workers at an automobile assembly plant, correlates with increased neurological disease, and, noticed in particular, an association with increased prevalence of a condition closely

resembling MS (52). Cavalleri et al. (1994) obtained results to indicate deterioration of colour vision in factory workers following perchloroethylene exposure, even at low levels (53), and Boor et al. (1977) confirm a damaging effect of toluene on the CNS (54), a chemical that is also known to effect CNS development prenatally (3). Alcohol (Ethanol) is a major environmental solvent, although exposure rarely occurs occupationally, and it is most often taken in voluntarily (3). Hommer et al. (2001) studied the brain volumes of alcoholic and non-alcoholic men and women, and found that alcoholics had a much smaller volume of grey matter than non-alcoholics.

This difference was found to be much more significant in females than males, suggesting an increased susceptibility of females to neurotoxic effects of alcoholism (34). In contrast, Pfefferbaum et al. (2001), in the same journal publication, indicated that the results of their study into alcohol effects on brain structure, show larger cortical sulci and lateral and third ventricles found in the alcoholics compared to non-alcoholics, which was a much greater and more significant difference in male subjects than female subjects. They also note that female brains show quicker and more effective recovery than those of males during abstinence (35). Jacobson (1986) carried out a study examining the brains of male and female alcoholics compared to non-alcoholic controls. It was noticed that the appearance of the brains on a CT scan was different between alcoholics and controls. Also observed was the fact that females appear more susceptible to structural changes in the brain following chronic alcohol intake, but are much more effective at recovering following cessation of intake, and the recovery occurs much quicker (80). Taking these 3 reports into consideration, there may be a difference in susceptibility of particular brain areas in males and females; however, females consistently recover more quickly from damage than males, indicating perhaps, a decreased susceptibility to long term damage. Neurophysiological deficits have also been reported in numerous studies of children exposed to alcohol pre-natally (81-83). However, few have noted results separately for male and female children.

Nanson and Hiscock (1990) observed that female Fetal Alcohol Syndrome (FAS) children appear to have a higher IQ than males with FAS (83). As mentioned above, the majority of studies into other solvents, such as toluene, trichloroethene, n-hexane, chlorinated solvents (84), and solvent mixtures (49, 50, 76, 78, 85) in the workplace, report an obvious detrimental effect on the CNS, PNS, or both, following exposure. However, the majority

included only men in the reports, or male and female results were analysed together. Again, it has been observed that the developing NS is especially susceptible to the neurotoxic effects of solvents, due to their high affinities for the brain's lipid tissues (33, 79), and the BBB not being fully formed (7). Laslo-Baker et al. (2004) and Till et al. (2001) carried out studies on organic solvent exposure in pregnant women, taken in accidentally from occupational exposure, and the effects on neurodevelopment of their offspring. Both groups confirmed that children exposed pre-natally had poorer cognitive functioning than those not exposed, with lower results in neurological tests (75, 86). Again, no distinction was made between results for female and male children. Considering the obvious effects of solvents, including alcohol and toluene, on the NS, and the observations of sex differences from other neurotoxins, and the implications of sex differences in effects of alcohol mentioned here, it should be suggested that future studies automatically investigate male and female results separately, and allow for observation of any differences in results.

Pesticides The term pesticides encompasses a wide range of chemicals, commonly used within a wide range of industries, particularly agriculture (87, 88). Included are the sub-groups; organophosphates, organochlorines, fumigants, and herbicides, all of which act to damage the NS of an organism, either directly, or via alteration of the cellular mechanisms that support it (87). Pesticides cause concern for human health as they are extremely widely used, and so readily released into the environment (88). It has been known for a long time that exposure to certain levels of these chemicals will adversely affect the human NS, as well as those organisms they are designed against (87, 88). Indeed, numerous studies have linked exposure to various pesticides with a number of neurological disorders, including Parkinson's disease (87, 89). In a similar situation to that for metals and solvents, there are many publications from groups investigating the effects of pesticide exposure on the human Nervous System, using an array of cognitive and neurobehavioural tests, with almost every study confirming the presence of some form of Neurotoxicity in subjects exposed to a range of doses. The following reports have identified separate results for neurological effects of pesticide exposure on male and female subjects, and an apparent greater effect on males. A report investigating the influence on the onset of Parkinson's and Alzheimer's Diseases in elderly people living in the south of France, where pesticides are used daily in vineyards, noted a significant association between these disorders and pesticide exposure, in males only (90), suggesting a potentially increased

susceptibility to males. Stallones et al. (2002) acknowledge males being at increased risk of developing neurological problems related to pesticide exposure than females, in an investigation into farmers, and their families in Colorado, USA (91), with the percentage of illnesses caused by exposure to pesticides almost three times greater in males. An assessment of neurobehavioural activity of Hispanic agricultural workers (92) identified a significant difference between the genders on results for 2 out of 10 tests, with females scoring lower than males. In the remaining tests, no significant differences were found between the sexes, although all exposed subjects faired worse than control, non-exposed (92). Similarly, pesticide-exposed Ecuadorians achieved lower outcomes in neurobehavioural tasks set by Cole et al. than did non-rural, unexposed Ecuadorians, and females were found to respond better in one task, with no significant difference between genders in others (93, 94). Guillette et al. (1998), carried out an assessment of Preschool children in Mexico, exposed to pesticides through living in close proximity of farm land. They identified a significant difference between those exposed and those living further away from the farm lands, with females performing better than males in several of the neurological tests (95). It appears that when there is a gender difference observed in the neurotoxic effects of pesticides, females tend to fair better than males, implying an increased susceptibility of males to the influences of pesticides on the NS. As it is more commonly males that are in the closest proximity to pesticides, within farming industries in particular, this could have some influence on this hypothesis.

However, as the differences are also apparent in male and female children, with equal exposure, it does indicate a greater risk for males. The finding that there was only a significant difference in some tests may indicate an increased susceptibility of some brain areas in males over others, which correlates with results of studies of alcohol and tobacco smoke (below). Other Sources of Environmental Neurotoxicity Tobacco Smoke The chemicals contained in tobacco smoke, particularly nicotine, are now known to cause a variety of neurological problems, in addition to their other effects, including behavioural and cognitive problems during development, tremor, and an increased risk of stroke, from both smoking directly, and through passive smoke; inhalation or exposure prenatally (96-100). Various groups investigating toxicity caused by intake of tobacco smoke have described minor sex difference in the neurological outcome. Louis (2007) reports that, when looking into hand tremor as an outcome of tobacco smoking, the difference in score between smokers and non-smokers is greater in women

than in men, which would indicate more of a susceptibility to women, rather than men (96). Jacobsen et al. (2007) investigated auditory and visual attention in adolescent smokers and non-smokers, with and without prenatal exposure to tobacco (101). They observed that different areas of the brain are apparently affected differently in male and female subjects exposed to tobacco smoke. In females, both auditory and visual attentions appear equally vulnerable, performing slightly more poorly in visual tests than males, while in males, auditory attention seems significantly more affected than visual attention, and in this auditory test, males performed substantially worse than females (101). The results of this investigation, put together with those from the Louis (2007) report, point towards sex-specific variations in neurotoxicity of particular areas of the NS. Cocaine Prenatal exposure to cocaine may be linked with an increase in aggressive behaviour at 5 years of age in boys, but no difference in girls (102). The data on sex differences in cocaine effects in humans is limited, and should be investigated further. Endocrine Disrupting chemicals Polychlorinated Biphenyls PCBs were once used widely industrially (21). They bio accumulate within animals, and get into the diet of humans (21, 103), which is known to lead to neurotoxic effects. Again, the developing CNS is particularly vulnerable, and a difference between effects in males and females had been noted in a number of studies. In adults, Needham et al. (2005) identified a difference between males and females in serum levels of PCBs, which is dependent upon the particular form of PCB. That is, pepta-PCB levels were higher in females, while levels of hepta-PCBs were higher in males (104). There is no link between these results and an increased susceptibility for either males or females. In children, in an investigation by Guo et al. (2004), into the neurological effects of prenatal exposure to PCBs, it was noticed that exposed boys showed problems with spatial reasoning, while girls did not.

Other tests, such as IQ, and movement, showed lower responses in exposed subjects, but no significant differences between the sexes (105). An assessment of play behaviour of a group of Dutch children exposed to PCBs prenatally (103) observed boys exposed prenatally to PCBs appear to have less masculinised play behaviour, while exposed girls had slightly more masculine behaviour (i.e. more aggressive, preference for male toys, lowered interest in appearance), although this was not as significant a result as for boys. The results appear to suggest a slightly higher susceptibility of boys to the neurotoxicity of PCBs, with poorer outcomes in certain tests.

Diethylstilbesterol In reports by Kester et al. (1980), and Lish et al. (1991, 1992) into playing behaviour of males and females, respectively, following prenatal exposure to DES (a synthetic oestrogen mimic), it can be noticed that, while males had increased masculine behaviour, no change in behaviour was observed in females (106-108). Exposure to DES prenatally has an influence on sexual differentiation of the brain, and cause masculinised behaviours in female rats, and demasculinised behaviour in male rats (26). Polybrominated Biphenyls An analysis of both male and female residents of an American dairy farming town exposed to polybrominated biphenyls, through eating contaminated animals, indicates neurotoxicity in these individuals, with lower outcomes in neurological tests than control individuals, from an alternative town, without exposure (109). This report also shows that females performed significantly better than males in all three tests carried out, indicating again than males may be more susceptible to this neurotoxicity (109, 110). Table 1 shows a summary of the environmental chemicals mentioned here, the amount of evidence of sex differences, some of the proposed mechanisms of action, sources of environmental exposure, and whether differences have been observed in adults or children. The observed differences in the effects of these environmental chemicals in humans, along with similar results observed within studies on animals, suggest an increased susceptibility to neurotoxicity for males than females. The differences between the sexes observed and put forward here indicate a greater susceptibility for males than females to the neurotoxic effects of environmental chemicals. The relatively small amounts of evidence, for a small number of the vast amounts of neurotoxic chemicals known, is not necessarily because differences between males and females are not a factor, but may be due to the fact that analysing results for males and females individually is not seen as an important factor to investigators, meaning all results, male and female, are analysed together. If in fact, as the reports here suggest, there is a difference between the sexes in susceptibility to neurotoxic effects, it is important for future studies to acknowledge males and females separately.

Indeed, this sex difference may be specific to certain chemicals, and this must be clarified as it may be due to a specific mechanism of action of different chemicals. Table 1. Summary table of the neurotoxic environmental chemicals included in this report, how much evidence there is of a sex difference in susceptibility to neurotoxicity (a greater number of + signs indicates more conclusive evidence), some of the proposed mechanisms of action of each chemical, exposure sources, and whether neurotoxicity and sex differences have been observed mainly in

adults, children, or both. Numerous animal studies, support this indication of a sex difference. Studies in rats and mice show that following prenatal methylmercury exposure, young male rats have significantly decreased responses to stimulation of dopamine receptors (114), while females do not, and locomotor function is affected more in young male rats than females (115). It has also been reported that there is a decrease in locomotor activity following lead exposure in Drosophila melanogaster. The difference in activity between exposed animals and controls is much more significant in males than in females (116). Various animal investigations of the neurotoxicity of manganese identify different areas of the brain which are more seriously affected in males and females following manganese exposure (117). Lower levels of the enzyme glutamine synthetase associated with manganese exposure have been found in the hippocampus, cerebellum, and olfactory bulb of male rats, and in the hypothalamus of females (117). Manganese is also transported to different areas of the male and female brains, of birds (118), with faster manganese transport in males (118). It has been noted that rats exposed to solvents have a decreased memory capacity than control, unexposed rats; a difference that was much more significant in males than females (119, 120). Nicotine exposure in adolescent rats induced an increase in the expression of genes associated with cell death p53 and c-fos.

There were differences between the genders in the areas of neurotoxicity, with greater toxic effects in the cerebral cortex of males than females, and greater effects in the hippocampus of females (120). A number of animal studies support the implication of a sex difference in PCB neurotoxicity. Female rats exposed to PCBs (25), show masculinised behaviour, and a greater performance on various motor tests than males (121). The volume of the cerebellum was also found to be smaller in males, following PCB exposure (121). Other studies report a sex difference in neurotoxicity with effects on spatial learning being more detrimental in male rats (122, 123). Sex differences have been observed in animal studies of other neurotoxins also, which indicates an importance in future human neurotoxicity studies looking into gender differences. Following insult from a dopaminergic neurotoxin, female rodents appear more protected from neurotoxicity than males (124). Sex differences in dopamine and serotonin depletions related to methamphetamine toxicity, have been confirmed in various different strains of mice (125), males show greater deterioration of neurotransmitter systems than females following methamphetamine exposure (126). Sex differences There may be a number of reasons for this

difference between the genders, such as differences in levels and activities of metabolising enzymes, absorption of exogenous substances, and levels of transporting proteins available (6). CNS development is known to be much slower in males than in females (127). As CNS development is a period of particular vulnerability to environmental neurotoxicants, the naturally slower development in males may suggest another reason for differences in susceptibility. It may also be suggested that males are often exposed to greater amounts of chemicals than females, due to different hobbies, occupations, etc (6). However, similar differences noted in children and animals, where there is equivalent exposure, implies that there is a biological difference in susceptibility. The NS, and the brain in particular, differs between males and females of a species, which provides another reason for sex differences in neurotoxin effects, particularly since numerous studies have noticed a difference in outcomes in certain brain areas (101, 117, 118). Sexual differentiation and organisation of the brain and NS influenced by the action of the sex hormones (26). Due to the extent to which hormones influence the NS, it is reasonable to assume a role for these molecules in the differing susceptibilities of males and females.

Gender differences in NS structure Male brains tend to be larger than female, with a higher amount of grey matter and lower amount of white matter (128). Females, although their brains are smaller than males, in some brain areas, have higher densities of neurons than males, particularly in areas involved in judgement, planning and language (129). This may offer an explanation for differences in outcomes of certain tests, as males will suffer more from neuronal damage if there are a smaller number of neurons present to compensate. It has also been noted that parts of the frontal cortex and limbic cortex, involved in higher cognitive functions and emotion, respectively, are larger in female brains, while parts of the parietal cortex and the amygdala, involved in spatial awareness and response to emotional arousal, respectively, are larger in men (129). The volume of the hippocampus, which has large numbers of oestrogen and oestrogen-receptor synthesising enzymes, is larger in young girls than boys, while boys have a larger amygdala, which holds large numbers of androgen and androgen-receptor synthesising enzymes (130). This may be an important factor in gender differences, as hormones are potent neuroprotectors (as discussed in the following section) and so a greater number of receptors in a particular brain area will provide enhanced neuroprotection. The difference in brain morphology between the sexes results in differences in behaviour and intelligence (6), with, in general, females performing better in verbal

tasks, and males performing better in mathematical and spatial tasks (131), and having generally more aggressive behaviour (132). Neurotransmitter systems are known to be sexually dimorphic (133). In females, there are greater numbers of receptors and transporters for neurotransmitters in serotonergic, dopaminergic, cholinergic and GABAergic, meaning greater functioning and more efficient signal transmission in women (130). Therefore, as the majority of chemicals affect the neurotransmitter systems, the female NS will be better able to cope and compensate for toxic damage. As previously mentioned, a key influence on the differentiation of the brain and NS into a particular sex, and subsequent development of the system, are the actions of hormones (26). Oestrogen, in particular, influences organisation of brain areas. The brain is innately female and differentiation of male brains is caused by testosterone conversion to oestrogen by the enzyme aromatase (26). The SRY gene found on the Y chromosome causes differentiation of the testes, which causes substantial amounts of testosterone to be released. The higher amounts of testosterone present contribute to differentiation to a male brain (127). The levels of different hormones determines numbers of neurons, organisation of synapses and dendrite structure within the brain, and causes the differences between male and female brains (26). The hormonal influence on the CNS, and the resulting differences in brain structure, may offer a suggestion about the differences between the genders concerning onset of certain neurological conditions, for example Parkinson's and Alzheimer's disease, to which men would appear more susceptible, and depression, to which women appear more susceptible (134-137). In addition to the role they play during development, hormones also have a continuous influence on neuronal systems, affecting growth of neurons, and playing a part in neuroprotection from insults. Hormones and Neuroprotection The remainder of this report will look at the gonadal hormones and their effects on neuronal survival and function as a reason for differing susceptibility between men and women.

Sex hormones, and their metabolites, have a wide range of roles within the human system, outside and unrelated to their important roles in reproduction (138). Figure 1 shows the structures of each of the three main sex hormones, and how they are related. Figure 1. Structures of the 3 main steroid sex hormones.

Note the phenolic A ring of Oestrogen that is not present within progesterone or testosterone, and the presence of a methyl group at carbon 17 on progesterone and testosterone, but not oestrogen. Adapted from diagrams in

(139). These molecules, in particular the female sex hormone oestrogen, are thought to have an important role in neuroprotection from toxic insults. Oestrogen Oestrogen is known to aid growth and survival of neurons during development of the CNS. The notion that oestrogen may have a protective role within the NS arose from animal studies of brain injury, with an indication of a sex difference in the response (135), and less severe damage in female animals (135). Women are also at lower risk of neurological diseases, such as stroke, throughout life, until the menopause when oestrogen levels drop (135), and neuroprotection appears to vary throughout the monthly oestrous cycle (124, 125, 140). Further in vivo studies on animals, and in vitro cell culture studies, have strengthened the theory of neuroprotection by oestrogen. Ovariectomy of female rodents abolishes protection from damage within the brain following stroke (141), and administration of exogenous oestrogen to female and male rodents reduces the damage caused (142). Administration of oestrogen to gonadectomised rodents treated with potent neurotoxins, such as domoic acid (143), kainic acid (144), and methamphetamine, resulted in reduced cell death by these substance and improved neurotransmission (124, 145). Oestrogen treatment improves survival of SK-N-SH human neuroblastoma cells, and cerebral cortex explants in culture, after exposure to certain toxic substances (134, 146). A protective action, rather than mitotic action of oestrogen has been confirmed, as without insult, oestrogen does not cause an increase in cell number (147), and following toxic insult, the ratio of dead cells to surviving cells is lowered (148). Oestrogen is thought to act directly on neuronal cells, and indirectly, via astrocytes, endothelial cells, and microglia, and a wide range of protective mechanisms have been proposed.

Below is a brief overview of some of the mechanisms by which oestrogen mediates its neuroprotection. Figure 2 shows a summary diagram of the main mechanisms. More detailed explanations are provided by review references: (134, 135, 137, 149). Figure 2. A summary diagram of the main mechanisms of oestrogen neuroprotection. A – Mechanisms of action via oestrogen receptors, including activation of second messenger signalling systems, and activation of gene transcription for anti-apoptotic proteins. B – Oestrogenic influence on other cells within the NS. C – Antioxidant action of oestrogen; interacting with and stabilising free radicals, and inhibition of free radical production by mitochondria. D – Influence on intracellular calcium levels; increase via activation of channels, and decrease via sequestration into mitochondria. E – Effects on neuronal growth and differentiation; interaction with neurotrophins. F – Action on neurotransmitter systems; blockage of re-uptake,

blockage of transport channels to prevent neurotoxin entry, inhibition of neurotransmitter metabolising enzymes. Adapted from diagrams within (135, 150). Oestrogen receptors (Figure 2- A) Oestrogen interacts with receptors expressed by neuronal cells to cause increased or reduced expression of certain genes, and to activate various signalling pathways. A number of oestrogen receptors have been identified, differing slightly in structure, and in expression in different tissues and tissue areas (5, 150). The use of antagonists (134, 151, 152), and agonists (153) of oestrogen receptors, in particular oestrogen receptors ? and ? (153), has confirmed their role in neuroprotective mechanisms. Oestrogen-oestrogen receptor interaction has been shown to cause increased expression of anti-apoptotic proteins, such as Bcl-2 and Akt, and inhibit the expression of pro-apoptotic proteins, such as BAD, cytochrome c and calpain, and alter activity of other specific targets (134, 153-155). This action can be direct via nuclear receptor interactions with genes, and/or indirect, via activation of signalling pathways, such as the cAMP-PKA-CREB pathway (149), and the mitogen activated protein kinase (MAPK) signal transduction pathway (144). Bcl-2 and Akt are anti-apoptotic proteins, that inhibit production of free radicals, regulate cellular calcium levels, inhibit the activation of pro-apoptotic proteins such as BAD, and prevent activation of a cascade of caspases that can lead to apoptosis (153, 154). Bains et al. 2007, have also confirmed a protective role for oestrogen via oestrogen receptors, to influence surrounding glial cells (astrocytes and microglia) (152). Other cells influenced by oestrogen (Figure 2- B) Oestrogen is thought to have an effect on neuronal protection indirectly, by acting on alternative cells within the NS, influencing processes within them, which then act on neurons to increase survival (135). Oestrogen has been shown to act on astrocytes (156, 157), to stimulate release of neurotrophic factors from these cells (135), increase the activity of glutamine synthetase, an enzyme essential for production of glutamine, taken up by neurons and used to make the neurotransmitter glutamate (135), and stimulate production of oestrogen locally via conversion of testosterone within astrocytes by aromatase (143, 158). Oestrogen is also known to act on microglial cells (specialised macrophages in the brain), and prevent their release of inflammatory mediators, such as cytokines (137, 159), and free radicals (134), which are implicated in the degenerative process of many common neurological problems, such as stroke and Alzheimer's disease (160). Antioxidant activity (Figure 2- C) Free radicals, such as Reactive Oxygen Species (ROS), are often produced in neuronal cells following injury induced by toxic substances and molecules (135, 161, 162), playing a major role in damage and death of these cells. It is thought that oestrogen is able to reduce the production of these free

radicals, limiting extensive damage to neurons (135, 161, 162). There is a large amount of evidence indicating oestrogen has anti-oxidant activity against these species (161, 163). Oestrogen reduces production of free radicals within the mitochondria of a cell, where it also acts to maintain the membrane potential, and prevent ATP depletion, following neuronal damage (151). The hormone can also act as a scavenger, trapping and stabilising free radicals so they can no longer react within a cell to cause damage (136). Oestrogen appears to be the only steroid molecule that can exert this action, due to the specialised phenolic A ring contained within the structure of the oestrogen steroid molecule (Figure 1) (136, 147, 162). The necessity for a phenolic A ring to be present has been confirmed in studies showing antioxidant activity is not observed with congeners of oestrogen, lacking this structure (164). As oestrogen has a phenolic A ring, and the male hormone, testosterone does not, this implies a reason for sex differences in neurotoxicity. It is reported often that higher levels of oestrogen needed to carry out antioxidant action than other mechanisms of neuroprotection (149-151, 155, 161, 163), indicating a possible link with sex differences observed in those chemicals where oxidative stress is a mechanism, as females have much higher natural levels of oestrogen than males.

Calcium (Figure 2- D) Oestrogen has been observed as having dual, and in fact, opposing, roles in modulating calcium (Ca^{2+}) levels in response to neurotoxic insults. Firstly, it has been shown that oestrogen treatment can induce an increase in intracellular Ca^{2+}levels, via interaction with oestrogen receptors and others, such as the NMDA receptors, to cause opening of Ca^{2+} influx channels, and release from ER stores, in order to protect against neuronal damage (149, 165). This rise in intracellular Ca^{2+} levels, results in activation of second messenger signalling cascades, leading to the activation of proteins such as CREB, which play a role in generation of dendritic spines of neurons (165). However, certain mechanisms of neurotoxicity, cause a rapid and substantial rise in intracellular Ca^{2+} levels, which can lead to extensive damage and cell death (149). In these circumstances, oestrogen acts to prevent this rise, so limiting any damage resulting from high Ca^{2+} levels (161, 166), via blockage of Ca^{2+} channels, preventing entry into the cell, and sequestration of Ca^{2+} into mitochondria (167). Normally, uptake of Ca^{2+} into mitochondria in large amounts is considered as an aspect of toxicity, as it can lead to altered membrane potential, triggering cell death. However, it is thought that the oestrogen induced activation of Bcl-2 (mentioned earlier), increases the capacity of mitochondria for reuptake of Ca^{2+}(166). Neuronal Growth and

Differentiation (Figure 2- E) In addition to the protection of mature neurons, following neurotoxic insult, oestrogen has been shown to influence the proliferation and specific migration of new neurons within the brain, encouraging newly proliferated cells to migrate to the damaged site and aid recovery and repair (134, 168). It is also known to affect the morphology of neurons, increasing the density of dendritic spines and formation of new synapses (140, 148, 151, 167, 168). The rise in Ca2+ within the cell(168), and activation of cellular proteins (151), induced by oestrogen following toxic insult, are thought to initiate many of the signalling events regulating the growth of neurons, and formation of synapses (165, 168). Interactions with Neurotrophins: Neurotrophins, such as Nerve Growth Factor (NGF), and Brain Derived Neurotrophic Factor (BDNF), are molecules that stimulate neuronal growth and differentiation. Oestrogen stimulates their release from astrocytes, activates, and works alongside these factors, to enhance development of neurons (136, 138). It has been noted that both oestrogen and neurotrophin receptors can be found on the same neurons, and so it is thought that the ligands for each receptor may be able to interact with either receptor, allowing oestrogen to have an effect on neuronal growth genes (136). Neurotransmitter systems (Figure 2- F) Within neurotransmitter systems, oestrogen modulates the effects of key enzymes for synthesis and degradation of neurotransmitter molecules (148), and affects the numbers and affinities of receptor molecules for neurotransmitters at the synaptic membrane (136, 137). It influences neurotransmitter transporters, by blockade (138, 145) and prevention of activation via second messenger signalling (169), in order to protect neurons against neurotoxins entering the cell by the use of these transporters.

Effects on the transporter molecules also provide decreased transmitter reuptake, thereby prolonging the action at the synapse (145). All neurotransmitter systems are readily influenced by oestrogen (136, 137, 151). Norbury et al. (2003) provide more in depth detail about specific oestrogenic actions in serotonergic, noradrenergic, dopaminergic, and cholinergic systems (136). Other ways by which oestrogen can exert its neuroprotctive effects include; increasing cerebral blood flow, providing quicker and more efficient neurotoxin elimination (138, 145); increasing the expression of apolipoprotein E, which is involved in lipid transport during repair of neurons, influencing neuronal membrane potential to affect movement of ions, important for signal transduction (137); and causing a reduction in body temperature (females only in mice studies), as increased body temperature

enhances neurotoxicity (124, 138). The exact mechanisms of this are not clear. The mechanisms of neuroprotection by oestrogen are probably dependent on the mechanisms of neurotoxicity of a particular chemical. For example; the influence on intracellular Ca2+ levels of oestrogen will help protect against the Ca2+ homeostasis disruption of lead; the induction of neuronal proliferation and migration will help combat the prevention by mercury; and the antioxidant activity of oestrogen will help against free radical production by many environmental chemicals (7, 11-14, 16-18). It is evident that the neuroprotective mechanisms of oestrogen are complex, and most likely involves a combination of factors, depending perhaps on the type of insult, and the area of neurotoxicity within the Nervous System. Oestrogen is present at much higher levels within females than males, so oestrogen neuroprotection will be more efficient in females. It has also been observed that oestrogen has differing effects within male and female animals, depending on the area and systems affected (151, 170). For example, cholinergic neurons in the basal forebrain of male rats do not respond to oestrogen therapy in the same way as those of the female (151), however, no sex differences are noted in the induction of serotonin receptors within the hypothalamus of macaque monkeys (171). Females are thought to be more receptive to the neuroprotective actions of oestrogen, as higher doses of oestrogen treatment is required in male rodents in order to achieve neuroprotection (124, 172). As mentioned earlier, numerous brain regions contain higher numbers of oestrogen receptors, and larger amounts of oestrogen-synthesising enzymes in females brains (130). There is also evidence to suggest that oestrogen may actually enhance neurotoxic effects when administered to male mice (124, 172). Oestrogen diminishes the neurotoxic effects of methamphetamine within the NSDA system, in females only (124). This might provide an indication of a reason for sex differences in the effects of neurotoxins. Oestrogen is neuroprotective throughout in females, however if a particular neurotoxin affects an area where oestrogen is not neuroprotective within males, there will be a difference in outcome.

Progesterone There is some evidence reported for a protective role of progesterone within the NS (173-175), and a number of mechanisms of this neuroprotection have been proposed, such as; regulation of cell survival via alteration of neurotrophin expression, interaction with GABAA receptors to alter chloride currents across cell membranes and prevent cell death, and activate signalling systems to regulate transcriptions of anti-apoptotic genes (173). However, the studies into neuroprotection of progesterone are sparse, and the evidence is not nearly

as extensive as that for oestrogenic neuroprotection. There is also conflicting evidence, with many studies indicating no neuroprotection from progesterone (159, 162, 164, 167, 176), some confirming only a small indication of neuroprotection (161), and others stating an antagonistic effect of progesterone on the neuroprotective actions of oestrogen (155, 161, 177, 178). In addition, the stimulation of growth factors by oestrogen mentioned earlier, to influence neuronal growth and differentiation, within ovariectomised rats, is opposed when progesterone is administered, with the levels of growth factors remaining similar to controls (177). Oestrogen neuroprotection against the effects of kainic acid was diminished in ovariectomised rats also treated with progesterone (178). Progesterone is another major female sex hormone, and may act to control oestrogen's influences on the NS within a normally functioning system.

More studies are required to confirm the effects of progesterone one way or another. Testosterone There is conflicting evidence regarding the role of testosterone in neuroprotection. Many studies report that testosterone has no effect on preventing damage induced by neurotoxins (124). Some indicating that testosterone may even enhance neurotoxic damage (126, 170), whereas others report evidence for a minor neuroprotective role for testosterone and its metabolites (143, 158, 179, 180). It is known that testosterone is converted to oestrogen within the Nervous System via the action of a specialised enzyme known as aromatase (181). Many studies indicate any protective effects of androgens within the CNS are dependent on metabolism to oestrogen by aromatase (143, 158). Injection of the potent neurotoxins domoic acid and kainic acid to gonadectomised rodents significantly decreased the amount of hilar neurons in the dentate gyrus of the brain. This toxic effect was reduced significantly with pre-treatment of both oestrogen and testosterone.

However, dihydroxytestosterone, a testosterone metabolite that cannot undergo aromatisation to oestrogen, did not prevent the action of these chemicals (143). Furthermore, the use of an aromatase inhibitor; fadrazole, prevents the neuroprotective effects of testosterone (143). This indicates the need for conversion of testosterone to oestrogen, by the action of aromatase, in order to have a neuroprotective effect. An increase in aromatase levels have been observed in areas surrounding neurotoxic damage, resulting in increased local oestrogen levels, contributing to neuroprotection (143, 158). If this is the case, it might provide a reason for sex differences, as

males would be required to produce oestrogen for protection, while females would already have high levels present, so neuroprotection would be much more efficient. There is some emerging evidence that testosterone may have a role in protection of neuronal cells, without first being converted to aromatase. In serum deprived cultured neuronal cells, testosterone was shown to significantly reduce the percentage of neuronal cell death (179). Similar results obtained from a non-aromatisable metabolite of testosterone, mibolerone, indicate a neuroprotective mechanism for testosterone, without aromatisation to oestrogen (179). Antagonists of androgen receptors diminish the neuroprotective effects of testosterone, implying a mechanism mediated via interaction with these receptors. This may be similar to that of oestrogen neuroprotection mediated through the oestrogen receptor (179); via activation of second messenger signalling systems, including the MAPK pathway, which promotes survival of cells (180), and phosphorylation, and therefore inactivation, of pro-apoptotic proteins such as BAD (180). Other mechanisms that have been suggested for testosterone-mediated neuroprotection include; prevention of hyperphosphorylation of tau, a neuron-damaging protein, decreased secretion of A? peptides, and increased expression of neurotrophic factors (182). These mechanisms are not as well studied as those for oestrogenic neuroprotection, and require further investigation. There is also an implication that neuroprotection by testosterone is specific to particular chemicals. While oestrogen exerts a general neuroprotective role throughout the Nervous System, against most neurotoxic insults, testosterone protects neurons from some forms of injury but not others (182). Following methamphetamine toxicity, oestrogen is shown to reduce damaging effects within dopaminergic, and serotonergic systems, while testosterone appears to have no effect, and in some cases, exacerbate the neurotoxicity (124-126, 138). This may support an indication of an increased susceptibility to neurotoxicity of certain chemicals for males.

Any observed neuroprotective effects of testosterone were also not as significant as those of oestrogen, which has been proposed to be due to the different structures of the molecules; the absence of a phenolic A ring within testosterones, and presence of a methyl group at carbon 17 (164, 179) (Figure 1). Oestrogen and testosterone can influence clearance of exogenous substances. Males have much slower clearance of perfluoroctanoic acid than females. Oestrogen treatment increases clearance, while testosterone reduces clearance (183). This may be another indication of a sex difference, as females may be able to clear chemicals from the system more efficiently

than males, providing less time for neurotoxic action. These observations all indicate a substantially greater neuroprotective activity for oestrogen than other hormones.

While testosterone may have a neuroprotective role, the actions appear to be specific to certain insults, and not as effective as those of oestrogen, and the mechanisms have not been well enough investigated as yet. As oestrogen is the main sex hormone of females, and testosterone of males, this provides a probable key reason for the difference in susceptibility to neurotoxins between the sexes. Hormonal neuroprotection as a reason for sex differences in response to neurotoxicity The role of hormones in neuroprotection described above provides a number of reasons for differing susceptibilities. The female sex hormone, oestrogen, is a powerful neuroprotectant, with much greater effect on neuronal survival, from a wider range of insults, than the male sex hormone, testosterone. While both hormones are present in both sexes, oestrogen levels are usually between 2 and 10 times higher in women than in men (124), which would imply a higher level of neuroprotection, therefore a lower level of susceptibility to neurotoxins, for females. The fact that testosterone promotes neuroprotection following some insults, and not others, while oestrogen has protective action against almost all neuronal damage, provides a suggestion to the differences in responses between males and females following certain neurotoxic exposures (124-126, 138), which may be linked to the specific mechanism of action of the chemical.

There is some evidence to suggest that aromatase activity may be greater in females than in males, therefore, female astrocytes are less susceptible to damage (158, 184). These levels did not alter upon induction of hypoxic conditions (184). Hormones are released from astrocytes (181), so, not only do females have higher natural levels of oestrogen, but may have a higher capacity to create further oestrogen to exert a neuroprotective action. The fact that in the majority of reports, a pre-treatment of oestrogen is required in order for maximum neuroprotection to occur, and limited effects are seen when administered after the neurotoxic insult has been exposed, may indicate a suggestion for the sex differences in response to neurotoxicity observed, as females have a much greater physiological level of oestrogen than men, who are required to convert testosterone to oestrogen for the majority of its neuroprotection to occur (152-154). Also, most studies indicate the need of higher amount of oestrogen in order for some of the neuroprotective actions to occur, such as the antioxidant activity, which may

suggest another reason for the sex differences (149-151, 155). It is also noted that males have fewer oestrogen receptors than females, due to the differences in NS structure between the sexes, and differences in certain brain areas, which may affect the neuroprotective capacity within male and female brains (130), and provide a reason for the differences in different brain areas observed in a number of studies (101, 117, 118). Conclusion Unfortunately, differences between genders have not been a priority for the majority of reports into neurotoxicity of environmental chemicals. As a result, studies published rarely indicate separate results for males and females, and many fail to include females in analyses at all.

Brains of males and females differ in many aspects under normal conditions. Due to this fact alone it would seem clear that it should be necessary to analyse results individually for each sex. The conclusions from many studies about the protective activity of hormones within the nervous system; that the female sex hormone oestrogen is confirmed as having various different neuroprotective actions against may different toxic insults, and the male hormone testosterone has only minor, insult specific effects, provides further reason to look more extensively into the differences between the sexes. This, together with the evidence that is available from several sources, with a difference in outcomes of neurological tests of males and females exposed to the same environmental chemicals, implies a greater susceptibility of males to their neurotoxic effects.

While there are hundreds of chemicals known to cause neurotoxicity, there are only a few mentioned in this report as showing any evidence of a gender difference in susceptibility. It may be that there are specific, common mechanisms of action, which result in gender differences in susceptibility to the effects of certain chemicals only. Those mechanisms may be those that are known to be protected against by the sex hormone oestrogen. However, it may be that other chemicals also induce a gender difference in response, which has not been noticed as there is a lack of separate male and female data. It may be that a gender difference in response to many more chemicals would be apparent if future investigations included gender differences as a priority for analysis. Many of the studies mentioned in this report have used child subjects. This may be mainly due to the fact that the majority of studies which provide both male and female results individually were carried out in children.

Male and female children are also more likely to have equal exposure to chemicals, and therefore it may be easier and more reliable to observe any differences. However, adult studies should also remember to separate male and female data. Hormone levels are known to change throughout life, and the variations in concentrations may influence sex differences due to the neuroprotection conferred by sex hormones. There is a clear need for future studies involved in neurotoxic effects of chemicals, to investigate gender differences, as this would appear to play a major important role in an individual's susceptibility to neurotoxicity.

References 1.Silverthorn, D. (2004) Neurons: Cellular and Network Properties. In Human Physiology – An Integrated Approach (Berriman, L., ed) pp. 239-283, Pearson Eductaion Inc 2.Toews, A. D., and Morell, P. (1999) Molecular Biological Approaches in Neurotoxicology. In Neurotoxicology (Tilson, H. A., and Harry, G. J., eds) pp. 1-35, Taylor and Francis 3.Grandjean, P., and Landrigan, P. J. (2006) Developmental neurotoxicity of industrial chemicals. Lancet 368, 2167-2178 4.Rice, D., and Barone, S., Jr. (2000) Critical periods of vulnerability for the developing nervous system: evidence from humans and animal models. Environmental Health Perspectives 108 Suppl 3, 511-533 5.Bryant, D. N., Sheldahl, L. C., Marriott, L. K., Shapiro, R. A., and Dorsa, D. M. (2006) Multiple pathways transmit neuroprotective effects of gonadal steroids. Endocrine 29, 199-207 6.Vahter, M., Gochfeld, M., Casati, B., Thiruchelvam, M., Falk-Filippson, A., Kavlock, R., Marafante, E., and Cory-Slechta, D. (2007) Implications of gender differences for human health risk assessment and toxicology. Environmental Research 104, 70-84 7.Costa, L. G., Aschner, M., Vitalone, T. S., and Soldin, O. P. (2004) Developmental Neuropathology of Environmental Agents.

Annual Review of Pharmacology & Toxicology 44, 87-110 8.Singer, R., and Johnson, D. D. (2006) Recognising Neurotoxicity Available at: https://www.neurotox.com/Recognizing_Neurotoxicity.doc last accessed: 21st January 2008 9.Sullivan, E. V., and Rosenbloom, M. (1999) Effects of Neurotoxins Revealed Through In Vivo Brain Imaging. In Neurotoxicology (Tilson, H. A., and Harry, G. J., eds) pp. 287-209, Taylor and Francis 10.Tilson, H. A., and Harry, G. J. (1999) Neurotoxicology, Taylor and Francis 11.Dobson, A. W., Erikson, K. M., and Aschner, M. (2004) Manganese neurotoxicity. Annals of the New York Academy of Sciences 1012, 115-128 12.Normandin, L., and Hazell, A. S. (2002) Manganese neurotoxicity: an update of pathophysiologic mechanisms.

Metabolic Brain Disease 17, 375-387 13.Lidsky, T. I., and Schneider, J. S. (2003) Lead neurotoxicity in children: basic mechanisms and clinical correlates. Brain 126, 5-19 14.Garza, A., Vega, R., and Soto, E. (2006) Cellular mechanisms of lead neurotoxicity. Medical Science Monitor 12, RA57-65 15.Tahti, H., Engelke, M., and Vaalavirta, L. (1997) Mechanisms and models of neurotoxicity of n-hexane and related solvents. Archives of Toxicology.

Supplement 19, 337-345 16.Savolainen, H. (1982) Neurotoxicity of industrial chemicals and contaminants: aspects of biochemical mechanisms and effects. Archives of Toxicology. Supplement 5, 71-83 17.Bressler, J., Kim, K. A., Chakraborti, T., and Goldstein, G. (1999) Molecular mechanisms of lead neurotoxicity. Neurochemical Research 24, 595-600 18.Counter, S. A., and Buchanan, L. H. (2004) Mercury exposure in children: a review. Toxicology and Applied Pharmacology 198, 209-230 19.Myers, G. J., Davidson, P. W., Cox, C., Shamlaye, C. F., Palumbo, D., Cernichiari, E., Sloane-Reeves, J., Wilding, G. E., Kost, J., Huang, L.-S., and Clarkson, T. W. (2003) Prenatal methylmercury exposure from ocean fish consumption in the Seychelles child development study.

Lancet 361, 1686-1692 20.Finkelstein, Y., Milatovic, D., and Aschner, M. (2007) Modulation of cholinergic systems by manganese. Neurotoxicology 28, 1003-1014 21.Schantz, S. L., and Widholm, J. J. (2001) Cognitive effects of endocrine-disrupting chemicals in animals. Environmental Health Perspectives 109, 1197-1206 22.Crisp, T. M., Clegg, E. D., Cooper, R. L., Wood, W. P., Anderson, D. G., Baetcke, K. P., Hoffmann, J. L., Morrow, M. S., Rodier, D. J., Schaeffer, J. E., Touart, L. W., Zeeman, M. G., and Patel, Y. M. (1998) Environmental endocrine disruption: an effects assessment and analysis. Environmental Health Perspectives 106 Suppl 1, 11-56 23.Filby, A. L., Neuparth, T., Thorpe, K. L., Owen, R., Galloway, T. S., and Tyler, C. R. (2007) Health impacts of estrogens in the environment, considering complex mixture effects.

Environmental Health Perspectives 115, 1704-1710 24.Amaral Mendes, J. J. (2002) The endocrine disrupters: a major medical challenge. Food & Chemical Toxicology 40, 781-788 25.Weiss, B. (2002) Sexually dimorphic nonreproductive behaviors as indicators of endocrine disruption. Environmental Health Perspectives 110 Suppl 3, 387-391 26.Miller, D. B. (1999) Endocrine Disruption: Estrogen, Androgen and the Nervous System. In Neurotoxicology (Tilson, H. A., and Harry, G. J., eds) pp. 201-218, Taylor and Francis 27.Factor-Litvak, P.,

Wasserman, G., Kline, J. K., and Graziano, J. (1999) The Yugoslavia Prospective Study of environmental lead exposure. Environmental Health Perspectives 107, 9-15 28.Grandjean, P., White, R. F., Nielsen, A., Cleary, D., and de Oliveira Santos, E. C. (1999) Methylmercury neurotoxicity in Amazonian children downstream from gold mining. Environmental Health Perspectives 107, 587-591 29.Bowler, R. M., Gysens, S., Diamond, E., Booty, A., Hartney, C., and Roels, H. A. (2003) Neuropsychological sequelae of exposure to welding fumes in a group of occupationally exposed men.

International Journal of Hygiene & Environmental Health 206, 517-529 30.Fielder, N., Kipen, H., Kelly-McNeil, K., and Fenskie, R. (1997) Long-Term Use of Organophosphates and Neuropsychological Performance. American Journal of Industrial Medicine 32, 487-496 31.Davidson, P. W., Palumbo, D., Myers, G. J., Cox, C., Shamlaye, C. F., Sloane-Reeves, J., Cernichiari, E., Wilding, G. E., and Clarkson, T. W. (2000) Neurodevelopmental outcomes of Seychellois children from the pilot cohort at 108 months following prenatal exposure to methylmercury from a maternal fish diet.

Environmental Research 84, 1-11 32.Jacobson, J. L., and Jacobson, S. W. (1999) Assessing Neurotoxicity in Children. In Neurotoxicology (Tilson, H. A., and Harry, G. J., eds) pp. 339-366, Taylor and Francis 33.White, R. F., and Proctor, S. P. (1997) Solvents and Neurotoxcicity. The Lancet 349, 1239-1243 34.Hommer, D. W., Momenan, R., Kaiser, E., and Rawlings, R. R. (2001) Evidence for a gender-related effect of alcoholism on brain volumes. American Journal of Psychiatry 158, 198-204 35.Pfefferbaum, A., Rosenbloom, M., Deshmukh, A., and Sullivan, E. (2001) Sex differences in the effects of alcohol on brain structure. American Journal of Psychiatry 158, 188-197 36.Cordier, S., Garel, M., Mandereau, L., Morcel, H., Doineau, P., Gosme-Seguret, S., Josse, D., White, R., and Amiel-Tison, C. (2002) Neurodevelopmental Investigations among Methylmercury-Exposed Children in French Guiana.

Environmental Research 89, 1-11 37.McKeown-Eyssen, G. E., and Ruedy, J. (1983) Methyl mercury exposure in northern Quebec. I. Neurologic findings in adults. American Journal of Epidemiology 118, 461-469 38.Bellinger, D., Leviton, A., and Sloman, J. (1990) Antecedents and correlates of improved cognitive performance in children exposed in utero to low levels of lead. Environmental Health Perspectives 89, 5-11 39.Wasserman, G. A., Liu, X.,

Lolacono, N. J., Factor-Litvak, P., Kline, J. K., Popovac, D., Morina, N., Musabegovic, A., Vrenezi, N., Capuni-Paracka, S., Lekic, V., Preteni-Redjepi, E., Hadzialjevic, S., Slavkovich, V., and Graziano, J. H. (1997) Lead exposure and intelligence in 7-year-old children: the Yugoslavia Prospective Study. Environmental Health Perspectives 105, 956-962 40.Wasserman, G. A., Liu, X., Parvez, F., Ahsan, H., Levy, D., Factor-Litvak, P., Kline, J., van Geen, A., Slavkovich, V., LoIacono, N. J., Cheng, Z., Zheng, Y., and Graziano, J. H. (2006) Water manganese exposure and children's intellectual function in Araihazar, Bangladesh. Environmental Health Perspectives 114, 124-129 41.Liou, H. H., Tsai, M. C., Chen, C. J., Jeng, J. S., Chang, Y. C., Chen, S. Y., and Chen, R. C. (1997) Environmental risk factors and Parkinson's disease: A case-control study in Taiwan.

Neurology 48, 1583-1588 42.Gorell, J. M., Johnson, C. C., Rybicki, B. A., Peterson, E. L., and Richardson, R. J. (1998) The risk of Parkinson's disease with exposure to pesticides, farming, well water, and rural living. Neurology 50, 1346-1350 43.Moretto, A., and Lotti, M. (1998) Poisoning by organophosphorus insecticides and sensory neuropathy. Journal of Neurology, Neurosurgery & Psychiatry 64, 463-468 44.Albers, J. W., Berent, S., Garabrant, D. H., Giordani, B., Schweitzer, S. J., Garrison, R. P., and Richardson, R. J. (2004) The effects of occupational exposure to chlorpyrifos on the neurologic examination of central nervous system function: a prospective cohort study. Journal of Occupational & Environmental Medicine 46, 367-378 45.Albers, J. W., Garabrant, D. H., Mattsson, J. L., Burns, C. J., Cohen, S. S., Sima, C., Garrison, R. P., Richardson, R. J., and Berent, S. (2007) Dose-effect analyses of occupational chlorpyrifos exposure and peripheral nerve electrophysiology.

Toxicological Sciences 97, 196-204 46.Bowler, R. M., Gysens, S., Diamond, E., Nakagawa, S., Drezgic, M., and Roels, H. A. (2006) Manganese exposure: neuropsychological and neurological symptoms and effects in welders. Neurotoxicology 27, 315-326 47.Mergler, D., Huel, G., Bowler, R., Iregren, A., Belanger, S., Baldwin, M., Tardif, R., Smargiassi, A., and Martin, L. (1994) Nervous system dysfunction among workers with long-term exposure to manganese. Environmental Research 64, 151-180 48.Rosenstock, L., Keifer, M., Daniell, W. E., McConnell, R., Claypoole, K., and Group., A. T. P. H. E. S. (1991) Chronic central nervous system effects of acute organophosphate pesticide intoxication. Lancet 338, 223-227 49.Ihrig, A., Dietz, M. C., Bader, M., and Triebig, G. (2005) Longitudinal study to explore chronic neuropsychologic effects on solvent exposed workers. Industrial Health 43, 588-596

50.Hakkola, M. (1994) Neuropsychological symptoms among tanker drivers with exposure to solvents.

Occupational Medicine 44, 243-246 51.Fidler, A. T., Baker, E. L., and Letz, R. E. (1987) Neurobehavioural effects of occupational exposure to organic solvents among construction painters. British Journal of Industrial Medicine 44, 292-308 52.Nelson, N. A., Robins, T. G., White, R. F., and Garrison, R. P. (1994) A case-control study of chronic neuropsychiatric disease and organic solvent exposure in automobile assembly plant workers.

Occupational & Environmental Medicine 51, 302-307 53.Cavalleri, A., Gobba, F., Paltrinieri, M., Fantuzzi, G., Righi, E., and Aggazzotti, G. (1994) Perchloroethylene exposure can induce colour vision loss. Neuroscience Letters 179, 162-166 54.Boor, J. W., and Hurtig, H. I. (1977) Persistent cerebellar ataxia after exposure to toluene. Annals of Neurology 2, 440-442 55.McKeown-Eyssen, G. E., Ruedy, J., and Neims, A. (1983) Methyl Mercury Exposure in Northern Quebec II. Neurological Findings in Children. American Journal of Epidemiology 118, 470-479 56.Grandjean, P., Weihe, P., White, R. F., and Debes, F. (1998) Cognitive Performance of Children Prenatally Exposed to “Safe” Levels of Methylmercury.

Environmental Research 77, 165-172 57.Marsh, D. O., Clarkson, T. W., Cox, C., Myers, G. J., Amin-Zaki, L., and Al-Tikriti, S. (1987) Fetal methylmercury poisoning. Relationship between concentration in single strands of maternal hair and child effects. Archives of Neurology 44, 1017-1022 58.McKeown-Eyssen, G. E., Ruedy, J., and Neims, A. (1983) Methyl mercury exposure in northern Quebec. II. Neurologic findings in children. American Journal of Epidemiology 118, 470-479 59.Cordier, S., Garel, M., Mandereau, L., Morcel, H., Doineau, P., Gosme-Seguret, S., Josse, D., White, R., and Amiel-Tison, C. (2002) Neurodevelopmental investigations among methylmercury-exposed children in French Guiana. Environmental Research 89, 1-11 60.Grandjean, P., Weihe, P., White, R. F., and Debes, F. (1998) Cognitive performance of children prenatally exposed to “safe” levels of methylmercury.

Environmental Research 77, 165-172 61.Holmes, A. S., Blaxill, M. F., and Haley, B. E. (2003) Reduced Levels of Mercury in First Baby Haircuts of Autistic Children. International Journal of Toxicology 22, 277-285 62.Kehrig, H. A., Malm, O., Akagi, H., Guimaraes, J. R., and Torres, J. P. (1998) Methylmercury in fish and hair samples from the Balbina Feservoir, Brazilian Amazon.[see comment]. Environmental Research 77, 84-90 63.Dietrich, K. N., Krafft, K.

M., Bornschein, R. L., Hammond, P. B., Berger, O., Succop, P. A., and Bier, M. (1987) Low-level fetal lead exposure effect on neurobehavioral development in early infancy. Pediatrics 80, 721-730 64.Pocock, S. J., Ashby, D., and Smith, M. A. (1987) Lead exposure and children's intellectual performance. International Journal of Epidemiology 16, 57-67 65.Vega-Dienstmaier, J. M., Salinas-Pielago, J. E., Gutierrez-Campos, M. d. R., Mandamiento-Ayquipa, R. D., Yara-Hokama, M. d. C., Ponce-Canchihuaman, J., and Castro-Morales, J. (2006) Lead levels and cognitive abilities in Peruvian children.

Revista Brasileira de Psiquiatria 28, 33-39 66.Counter, S. A., Buchanan, L. H., Rosas, H. D., and Ortega, F. (1998) Neurocognitive effects of chronic lead intoxication in Andean children. Journal of the Neurological Sciences 160, 47-53 67.Wasserman, G. A., Staghezza-Jaramillo, B., Shrout, P., Popovac, D., and Graziano, J. (1998) The Effect of Lead Exposure on Behaviour Problems in Preschool Children. American Journal of Public Health 88, 481-486 68.Bellinger, D., Leviton, A., Allred, E., and Rabinowitz, M. (1994) Pre- and postnatal lead exposure and behavior problems in school-aged children. Environmental Research 66, 12-30 69.Tong, S., Baghurst, P., McMichael, A., Sawyer, M., and Mudge, J. (1996) Lifetime exposure to environmental lead and children's intelligence at 11-13 years: the Port Pirie cohort study. BMJ 312, 1569-1575 70.Leviton, A., Bellinger, D., Allred, E. N., Rabinowitz, M., Needleman, H., and Schoenbaum, S. (1993) Pre- and postnatal low-level lead exposure and children's dysfunction in school. Environmental Research 60, 30-43 71.Needleman, H. L., and Gatsonis, C. A. (1990) Low-level lead exposure and the IQ of children. A meta-analysis of modern studies. JAMA 263, 673-678 72.Bouchard, M., Laforest, F., Vandelac, L., Bellinger, D., and Mergler, D. (2007) Hair manganese and hyperactive behaviors: pilot study of school-age children exposed through tap water.

Environmental Health Perspectives 115, 122-127 73.Dietz, M. C., Ihrig, A., Wrazidlo, W., Bader, M., Jansen, O., and Triebig, G. (2001) Results of magnetic resonance imaging in long-term manganese dioxide-exposed workers. Environmental Research 85, 37-40 74.Mergler, D., Baldwin, M., Belanger, S., Larribe, F., Beuter, A., Bowler, R., Panisset, M., Edwards, R., de Geoffroy, A., Sassine, M. P., and Hudnell, K. (1999) Manganese neurotoxicity, a continuum of dysfunction: results from a community based study.

Neurotoxicology 20, 327-342 75.Till, C., Koren, G., and Rovet, J. F. (2001) Prenatal exposure to organic solvents and child neurobehavioral performance. Neurotoxicology & Teratology 23, 235-245 76.Muijser, H., Geuskens, R. B. M., Hooisma, J., Emmen, H. H., and Kulig, B. M. (1996) Behavioural Effects of Exposure to Organic Solvents in Carpet Layers. Neurotoxicology and Teratology 18, 455-462 77.Williamson, A. M., and Winder, C. (1993) A prospective cohort study of the chronic effects of solvent exposure. Environmental Research 62, 256-271 78.Juntunen, J. (1993) Neurotoxic syndromes and occupational exposure to solvents.

Environmental Research 60, 98-111 79.Lees-Haley, P. R., and Williams, C. W. (1997) Neurotoxicity of chronic low-dose exposure to organic solvents: a skeptical review. Journal of Clinical Psychology 53, 699-712 80.Jacobson, R. (1986) The contributions of sex and drinking history to the CT brain scan changes in alcoholics. Psychological Medicine 16, 547-559 81.Conry, J. (1990) Neuropsychological deficits in fetal alcohol syndrome and fetal alcohol effects. Alcoholism: Clinical & Experimental Research 14, 650-655 82.Streissguth, A. P., Barr, H. M., and Sampson, P. D. (1990) Moderate prenatal alcohol exposure: effects on child IQ and learning problems at age 7 1/2 years. Alcoholism: Clinical & Experimental Research 14, 662-669 83.Nanson, J. L., and Hiscock, M. (1990) Attention deficits in children exposed to alcohol prenatally.

Alcoholism: Clinical & Experimental Research 14, 656-661 84.Ruder, A. M. (2006) Potential health effects of occupational chlorinated solvent exposure. Annals of the New York Academy of Sciences 1076, 207-227 85.Zaidi, S., Tiwari, R., Gandhi, S., Patel, K., Kumar, S., and Saiyed, H. (2006) Neurobehavioural Effects and Hormones Profiles among Spray Painters. Industrial Health 44, 93-97 86.Laslo-Baker, D., Barrera, M., Knittel-Keren, D., Kozer, E., Wolpin, J., Khattak, S., Hackman, R., Rovet, J., and Koren, G. (2004) Child neurodevelopmental outcome and maternal occupational exposure to solvents. Archives of Pediatrics & Adolescent Medicine 158, 956-961 87.Keifer, M. C., and Firestone, J. (2007) Neurotoxicity of pesticides.

Journal of Agromedicine 12, 17-25 88.Weiss, B., Amler, S., and Amler, R. W. (2004) Pesticides. Pediatrics 113, 1030-1036 89.Kanthasamy, A. G., Kitazawa, M., Kanthasamy, A., and Anantharam, V. (2005) Dieldrin-induced neurotoxicity: relevance to Parkinson’s disease pathogenesis. Neurotoxicology 26, 701-719 90.Baldi, I., Lebailly, P.,

Mohammed-Brahim, B., Letenneur, L., Dartigues, J.-F., and Brochard, P. (2003) Neurodegenerative diseases and exposure to pesticides in the elderly. American Journal of Epidemiology 157, 409-414 91.Stallones, L., and Beseler, C. (2002) Pesticide illness, farm practices, and neurological symptoms among farm residents in Colorado. Environmental Research 90, 89-97 92.Rohlman, D. S., Lasarev, M., Anger, W. K., Scherer, J., Stupfel, J., and McCauley, L. (2007) Neurobehavioral performance of adult and adolescent agricultural workers.

Neurotoxicology 28, 374-380 93.Cole, D. C., Carpio, F., Julian, J., and Leon, N. (1998) Assessment of peripheral nerve function in an Ecuadorian rural population exposed to pesticides. Journal of Toxicology & Environmental Health Part A 55, 77-91 94.Cole, D. C., Carpio, F., Julian, J., Leon, N., Carbotte, R., and De Almeida, H. (1997) Neurobehavioral outcomes among farm and nonfarm rural Ecuadorians.

Neurotoxicology & Teratology 19, 277-286 95.Guillette, E. A., Meza, M. M., Aquillar, M. G., Soto, A. D., and Garcia, I. E. (1998) An Anthropological Approach to the Evaluation of Preschool children Exposed to Pesticides in Mexico. Environmental Health Perspectives 106, 347-353 96.Louis, E. D. (2007) Kinetic tremor: Differences between smokers and non-smokers. Neurotoxicology 28, 569-575 97.Nelson, E. (2001) The miseries of passive smoking. Human & Experimental Toxicology 20, 61-83 98.Fergusson, D. M., Horwood, L. J., and Lynskey, M. T. (1993) Maternal smoking before and after pregnancy: effects on behavioral outcomes in middle childhood.

Pediatrics 92, 815-822 99.Bonita, R., Duncan, J., Truelsen, T., Jackson, R. T., and Beaglehole, R. (1999) Passive smoking as well as active smoking increases the risk of acute stroke. Tobacco Control 8, 156-160 100.Slotkin, T. A. (1998) Fetal nicotine or cocaine exposure: which one is worse? Journal of Pharmacology & Experimental Therapeutics 285, 931-945 101.Jacobsen, L. K., Slotkin, T. A., Mencl, W. E., Frost, S. J., and Pugh, K. R. (2007) Gender-specific effects of prenatal and adolescent exposure to tobacco smoke on auditory and visual attention. Neuropsychopharmacology 32, 2453-2464 102.Bendersky, M., Bennett, D., and Lewis, M. (2006) Aggression at age 5 as a function of prenatal exposure to cocaine, gender, and environmental risk. Journal of Pediatric Psychology 31, 71-84 103.Vreugdenhil, H. J. I., Slijper, F. M. E., Mulder, P. G. H., and Weisglas-Kuperus, N. (2002) Effects of perinatal exposure to PCBs and dioxins on play behavior in Dutch children at school age. Environmental Health

Perspectives 110, A593-598 104.Needham, L. L., Barr, D. B., Caudill, S. P., Pirkle, J. L., Turner, W. E., Osterloh, J., Jones, R. L., and Sampson, E. J. (2005) Concentrations of Environmental Chemicals Associated with Neurodevelopmental Effects in U.S. Population.

Neurotoxicology 26, 531-545 105.Guo, Y. L., Lai, T. J., Chen, S. J., and Hsu, C. C. (1995) Gender-related decrease in Raven's progressive matrices scores in children prenatally exposed to polychlorinated biphenyls and related contaminants. Bulletin of Environmental Contamination & Toxicology 55, 8-13 106.Kester, P., Green, R., Finch, S. J., and Williams, K. (1980) Prenatal 'female hormone' administration and psychosexual development in human males. Psychoneuroendocrinology 5, 269-285 107.Lish, J., Ehrhardt, A., Meyer-Bahlburg, H., Rose, L., Gruen, R., and Veridano, N. (1991) Gender-related behaviour development in females exposed to diethylstilbersterol (DES) in utero: an attempted replication. Journal of the American Acadamy of Child and Adolescent Psychiatry 30, 29-37 108.Lish, J. D., Meyer-Bahlburg, H. F., Ehrhardt, A. A., Travis, B. G., and Veridiano, M. P. (1992) Prenatal exposure to diethylstilbesterol (DES): childhood play behaviour and adult gender-role behaviour in women.

Archives of Sexual Behaviour 21, 423-441 109.Valciukas, J. A., Lilis, R., Wolff, M. S., and Anderson, H. A. (1978) Comparative neurobehavioral study of a polybrominated biphenyl-exposed population in Michigan and a nonexposed group in Wisconsin. Environmental Health Perspectives 23, 199-210 110.Ding, L., Murphy, M. B., He, Y., Xu, Y., Yeung, L. W. Y., Wang, J., Zhou, B., Lam, P. K. S., Wu, R. S. S., and Giesy, J. P. (2007) Effects of brominated flame retardants and brominated dioxins on steroidogenesis in H295R human adrenocortical carcinoma cell line. Environmental Toxicology & Chemistry 26, 764-772 111.Demirel, Y., Yilmaz, A., Gursoy, S., Kaygusuz, K., and Mimaroglu, C. (2006) Acute amitraz intoxication: retrospective analysis of 45 cases. Human & Experimental Toxicology 25, 613-617 112.Kamel, F., and Hoppin, J. A. (2004) Association of pesticide exposure with neurologic dysfunction and disease. Environmental Health Perspectives 112, 950-958 113.Kaiser, R., Marcus, M., Blanck, H. M., Naughton, M., Zhang, R. H., Henderson, A. K., Tolbert, P. E., Rubin, C. H., and Hertzberg, V. S. (2003) Polybrominated biphenyl exposure and benign breast disease in a cohort of US women.

Annals of Epidemiology 13, 16-23 114.Gim©nez-Llort, L., Ahlbom, E., Dar©, E., Vahter, M., ögren, S.-O., and

Ceccatelli, S. (2001) Prenatal exposure to methylmercury changes dopamine-modulated motor activity during early ontogeny: age and gender-dependent effects. Environmental Toxicology and Pharmacology 9, 61-70 115.Rossi, A. D., Ahlbom, E., Ogren, S. O., Nicotera, P., and Ceccatelli, S. (1997) Prenatal exposure to methylmercury alters locomotor activity of male but not female rats.

Experimental Brain Research 117, 428-436 116.Hirsch, H. V. B., Mercer, J., Sambaziotis, H., Huber, M., Stark, D. T., Torno-Morley, T., Hollocher, K., Ghiradella, H., and Ruden, D. M. (2003) Behavioral effects of chronic exposure to low levels of lead in Drosophila melanogaster. Neurotoxicology 24, 435-442 117.Erikson, K. M., Dorman, D. C., Lash, L. H., Dobson, A. W., and Aschner, M. (2004) Airborne manganese exposure differentially affects end points of oxidative stress in an age- and sex-dependent manner. Biological Trace Element Research 100, 49-62 118.Van der Linden, A., Verhoye, M., Van Meir, V., Tindemans, I., Eens, M., Absil, P., and Balthazart, J. (2002) In vivo manganese-enhanced magnetic resonance imaging reveals connections and functional properties of the songbird vocal control system. Neuroscience 112, 467-474 119.Hass, U., Ladefoged, O., Lam, H. R., Ostergaard, G., Lund, S. P., and Sinonsen, L. (2001) Behavioural effects in rats after prenatal exposure to dearomatized white spirit.

Pharmacology & Toxicology 89, 201-207 120.Trauth, J. A., Seidler, F. J., and Slotkin, T. A. (2000) An animal model of adolescent nicotine exposure: effects on gene expression and macromolecular constituents in rat brain regions. Brain Research 867, 29-39 121.Nguon, K., Baxter, M. G., and Sajdel-Sulkowska, E. M. (2005) Perinatal exposure to polychlorinated biphenyls differentially affects cerebellar development and motor functions in male and female rat neonates. Cerebellum 4, 112-122 122.Schantz, S. L., Moshtaghian, J., and Ness, D. K. (1995) Spatial learning deficits in adult rats exposed to ortho-substituted PCB congeners during gestation and lactation. Fundamental & Applied Toxicology 26, 117-126 123.Roegge, C. S., Seo, B. W., Crofton, K. M., and Schantz, S. L. (2000) Gestational-lactational exposure to Aroclor 1254 impairs radial-arm maze performance in male rats. Toxicological Sciences 57, 121-130 124.Dluzen, D. E., and McDermott, J. L. (2002) Estrogen, anti-estrogen, and gender: differences in methamphetamine neurotoxicity.

Annals of the New York Academy of Sciences 965, 136-156 125.Yu, L., and Liao, P. C. (2000) Sexual differences and

estrous cycle in methamphetamine-induced dopamine and serotonin depletions in the striatum of mice. Journal of Neural Transmission 107, 419-427 126.Myers, R. E., Anderson, L. I., and Dluzen, D. E. (2003) Estron, but not testosterone, attenuates methamphetamine-evoked dopamine output from superfused striatal tissue of female and male mice. Neuropharmacology 44, 624-632 127.Eme, R. F. (2007) Sex differences in child-onset, life-course-persistent conduct disorder. A review of biological influences. Clinical Psychology Review 27, 607-627 128.Haier, R. J., Jung, R. E., Yeo, R. A., Head, K., and Alkire, M. T. (2004) Structural brain variation and general intelligence.

Neuroimage 23, 425-433 129.Cahill, L. (2005) His brain, her brain. Scientific American 292, 40-47 130.Cosgrove, K. P., Mazure, C. M., and Staley, J. K. (2007) Evolving knowledge of sex differences in brain structure, function, and chemistry. Biological Psychiatry 62, 847-855 131.Bell, E. C., Willson, M. C., Wilman, A. H., Dave, S., and Silverstone, P. H. (2006) Males and females differ in brain activation during cognitive tasks. Neuroimage 30, 529-538 132.Susman, E. J., Inoff-Germain, G., Nottelmann, E. D., Loriaux, D. L., Cutler, G. B., Jr., and Chrousos, G. P. (1987) Hormones, emotional dispositions, and aggressive attributes in young adolescents. Child Development 58, 1114-1134 133.Becker, J. B. (1999) Gender differences in dopaminergic function in striatum and nucleus accumbens.

Pharmacology, Biochemistry & Behavior 64, 803-812 134.Suzuki, S., Brown, C. M., and Wise, P. M. (2006) Mechanisms of neuroprotection by estrogen. Endocrine 29, 209-215 135.Brann, D. W., Dhandapani, K., Wakade, C., Mahesh, V. B., and Khan, M. M. (2007) Neurotrophic and neuroprotective actions of estrogen: basic mechanisms and clinical implications.

Steroids 72, 381-405 136.Norbury, R., Cutter, W. J., Compton, J., Robertson, D. M., Craig, M., Whitehead, M., and Murphy, D. G. (2003) The neuroprotective effects of estrogen on the aging brain. Experimental Gerontology 38, 109-117 137.Henderson, V. W., and Reynolds, D. W. (2002) Protective Effects of Estrogen on Aging and Damaged Neural Systems. Hormones, Brain and Behaviour 4, 821-837 138.Dluzen, D. E. (2000) Neuroprotective effects of estrogen upon the nigrostriatal dopaminergic system. Journal of Neurocytology 29, 387-399 139.Berg, J. M., Tymoczko, J. L., and Stryer, L. (2002) The Biosynthesis of Membrane Lipids and Steroids. In Biochemistry (Berg, J.

M., Tymoczko, J. L., and Stryer, L., eds) pp. 715-743, W.H.Freeman & Company 140.Woolley, C. S., and McEwen, B. S. (1992) Estradiol mediates fluctuation in hippocampal synapse density during the estrous cycle in the adult rat.

Journal of Neuroscience 12, 2549-2554 141.Alkayed, N. J., Harukuni, I., Kimes, A. S., London, E. D., Traystman, R. J., and Hurn, P. D. (1998) Gender-linked brain injury in experimental stroke. Stroke 29, 159-165; discussion 166 142.Gibson, C. L., Gray, L. J., Murphy, S. P., and Bath, P. M. W. (2006) Estrogens and experimental ischemic stroke: a systematic review. Journal of Cerebral Blood Flow & Metabolism 26, 1103-1113 143.Azcoitia, I., Sierra, A., Veiga, S., Honda, S., Harada, N., and Garcia-Segura, L. M. (2001) Brain aromatase is neuroprotective. Journal of Neurobiology 47, 318-329 144.Azcoitia, I., Sierra, A., and Garcia-Segura, L. M. (1998) Estradiol prevents kainic acid-induced neuronal loss in the rat dentate gyrus. Neuroreport 9, 3075-3079 145.Dluzen, D. E., and Anderson, L. I. (1997) Estrogen differentially modulates nicotine-evoked dopamine release from the striatum of male and female rats.

Neuroscience Letters 230, 140-142 146.Ba, F., Pang, P. K. T., Davidge, S. T., and Benishin, C. G. (2004) The neuroprotective effects of estrogen in SK-N-SH neuroblastoma cell cultures. Neurochemistry International 44, 401-411 147.Green, P. S., Gridley, K. E., and Simpkins, J. W. (1998) Nuclear estrogen receptor-independent neuroprotection by estratrienes: a novel interaction with glutathione. Neuroscience 84, 7-10 148.Bishop, J., and Simpkins, J. W. (1994) Estradiol treatment increases viability of glioma and neuroblastoma cells in vitro. Molecular & Cellular Neurosciences 5, 303-308 149.Green, P. S., and Simpkins, J. W. (2000) Neuroprotective effects of estrogens: potential mechanisms of action.

International Journal of Developmental Neuroscience 18, 347-358 150.Lee, S. J., and McEwen, B. S. (2001) Neurotrophic and neuroprotective actions of estrogens and their therapeutic implications. Annual Review of Pharmacology & Toxicology 41, 569-591 151.McEwen, B. S. (2001) Invited review: Estrogens effects on the brain: multiple sites and molecular mechanisms. Journal of Applied Physiology 91, 2785-2801 152.Bains, M., Cousins, J. C., and Roberts, J. L. (2007) Neuroprotection by estrogen against MPP+-induced dopamine neuron death is mediated by ERalpha in primary cultures of mouse mesencephalon. Experimental Neurology 204, 767-776

153.Zhao, L., Wu, T.-W., and Brinton, R. D. (2004) Estrogen receptor subtypes alpha and beta contribute to neuroprotection and increased Bcl-2 expression in primary hippocampal neurons. Brain Research 1010, 22-34 154.Dubal, D. B., Shughrue, P. J., Wilson, M. E., Merchenthaler, I., and Wise, P. M. (1999) Estradiol modulates bcl-2 in cerebral ischemia: a potential role for estrogen receptors.

Journal of Neuroscience 19, 6385-6393 155.Garcia-Segura, L. M., Cardona-Gomez, P., Naftolin, F., and Chowen, J. A. (1998) Estradiol upregulates Bcl-2 expression in adult brain neurons. Neuroreport 9, 593-597 156.Dhandapani, K. M., Hadman, M., De Sevilla, L., Wade, M. F., Mahesh, V. B., and Brann, D. W. (2003) Astrocyte protection of neurons: role of transforming growth factor-beta signaling via a c-Jun-AP-1 protective pathway.

Journal of Biological Chemistry 278, 43329-43339 157.Sortino, M. A., Chisari, M., Merlo, S., Vancheri, C., Caruso, M., Nicoletti, F., Canonico, P. L., and Copani, A. (2004) Glia mediates the neuroprotective action of estradiol on beta-amyloid-induced neuronal death. Endocrinology 145, 5080-5086 158.Roselli, C. F. (2007) Brain aromatase: roles in reproduction and neuroprotection. Journal of Steroid Biochemistry & Molecular Biology 106, 143-150 159.Bruce-Keller, A. J., Keeling, J. L., Keller, J. N., Huang, F. F., Camondola, S., and Mattson, M. P. (2000) Antiinflammatory effects of estrogen on microglial activation. Endocrinology 141, 3646-3656 160.Czlonkowska, A., Ciesielska, A., Gromadzka, G., and Kurkowska-Jastrzebska, I. (2006) Gender differences in neurological disease: role of estrogens and cytokines.

Endocrine 29, 243-256 161.Goodman, Y., Bruce, A. J., Cheng, B., and Mattson, M. P. (1996) Estrogens attenuate and corticosterone exacerbates excitotoxicity, oxidative injury, and amyloid beta-peptide toxicity in hippocampal neurons. Journal of Neurochemistry 66, 1836-1844 162.Behl, C., Widmann, M., Trapp, T., and Holsboer, F. (1995) 17-beta estradiol protects neurons from oxidative stress-induced cell death in vitro. Biochemical & Biophysical Research Communications 216, 473-482 163.Gridley, K. E., Green, P. S., and Simpkins, J. W. (1997) Low concentrations of estradiol reduce beta-amyloid (25-35)-induced toxicity, lipid peroxidation and glucose utilization in human SK-N-SH neuroblastoma cells. Brain Research 778, 158-165 164.Green, P. S., Gordon, K., and Simpkins, J. W. (1997) Phenolic A ring requirement for the neuroprotective effects of steroids. Journal of Steroid Biochemistry

& Molecular Biology 63, 229-235 165.Zhao, L., Chen, S., Ming Wang, J., and Brinton, R. D. (2005) 17beta-estradiol induces Ca2+ influx, dendritic and nuclear Ca2+ rise and subsequent cyclic AMP response element-binding protein activation in hippocampal neurons: a potential initiation mechanism for estrogen neurotrophism.

Neuroscience 132, 299-311 166.Nilsen, J., and Diaz Brinton, R. (2003) Mechanism of estrogen-mediated neuroprotection: regulation of mitochondrial calcium and Bcl-2 expression. Proceedings of the National Academy of Sciences of the United States of America 100, 2842-2847 167.Singer, C. A., Rogers, K. L., Strickland, T. M., and Dorsa, D. M. (1996) Estrogen protects primary cortical neurons from glutamate toxicity. Neuroscience Letters 212, 13-16 168.de Lacalle, S. (2006) Estrogen effects on neuronal morphology. Endocrine 29, 185-190 169.Figlewicz, D. P., Patterson, T. A., Zavosh, A., Brot, M. D., Roitman, M., and Szot, P. (1999) Neurotransmitter transporters: target for endocrine regulation.

Hormone & Metabolic Research 31, 335-339 170.Gao, X., and Dluzen, D. E. (2001) The effect of testosterone upon methamphetamine neurotoxicity of the nigrostriatal dopaminergic system. Brain Research 892, 63-69 171.Sumner, B. E., and Fink, G. (1998) Testosterone as well as estrogen increases serotonin2A receptor mRNA and binding site densities in the male rat brain. Brain Research Molecular Brain Research. 59, 205-214 172.Gillies, G. E., Murray, H. E., Dexter, D., and McArthur, S. (2004) Sex dimorphisms in the neuroprotective effects of estrogen in an animal model of Parkinson's disease. Pharmacology, Biochemistry & Behavior 78, 513-522 173.Singh, M. (2006) Progesterone-induced neuroprotection. Endocrine 29, 271-274 174.Asbury, E. T., Fritts, M. E., Horton, J. E., and Isaac, W. L. (1998) Progesterone facilitates the acquisition of avoidance learning and protects against subcortical neuronal death following prefrontal cortex ablation in the rat.

Behavioural Brain Research 97, 99-106 175.Gonzalez Deniselle, M. C., Lopez Costa, J. J., Gonzalez, S. L., Labombarda, F., Garay, L., Guennoun, R., Schumacher, M., and De Nicola, A. F. (2002) Basis of progesterone protection in spinal cord neurodegeneration. Journal of Steroid Biochemistry & Molecular Biology 83, 199-209 176.Choi, Y. C., Lee, J. H., Hong, K. W., and Lee, K. S. (2004) 17 Beta-estradiol prevents focal cerebral ischemic damages via activation of Akt and CREB in association with reduced PTEN phosphorylation in rats.

Fundamental & Clinical Pharmacology 18, 547-557 177.Bimonte-Nelson, H. A., Nelson, M. E., and Granholm, A.-C. E. (2004) Progesterone counteracts estrogen-induced increases in neurotrophins in the aged female rat brain. Neuroreport 15, 2659-2663 178.Rosario, E. R., Ramsden, M., and Pike, C. J. (2006) Progestins inhibit the neuroprotective effects of estrogen in rat hippocampus. Brain Research 1099, 206-210 179.Hammond, J., Le, Q., Goodyer, C., Gelfand, M., Trifiro, M., and LeBlanc, A. (2001) Testosterone-mediated neuroprotection through the androgen receptor in human primary neurons. Journal of Neurochemistry 77, 1319-1326 180.Nguyen, T.-V. V., Yao, M., and Pike, C. J. (2005) Androgens activate mitogen-activated protein kinase signaling: role in neuroprotection.

Journal of Neurochemistry 94, 1639-1651 181.Garcia-Ovejero, D., Azcoitia, I., Doncarlos, L. L., Melcangi, R. C., and Garcia-Segura, L. M. (2005) Glia-neuron crosstalk in the neuroprotective mechanisms of sex steroid hormones. Brain Research – Brain Research Reviews 48, 273-286 182.Bialek, M., Zaremba, P., Borowicz, K. K., and Czuczwar, S. J. (2004) Neuroprotective role of testosterone in the nervous system. Polish Journal of Pharmacology 56, 509-518 183.Gochfeld, M. (2007) Framework for gender differences in human and animal toxicology. Environmental Research 104, 4-21 184.Heyer, A., Hasselblatt, M., von Ahsen, N., Hafner, H., Siren, A.-L., and Ehrenreich, H. (2005) In vitro gender differences in neuronal survival on hypoxia and in 17beta-estradiol-mediated neuroprotection. Journal of Cerebral Blood Flow & Metabolism 25, 427-430