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Invited Editorial

Environmental Xenobiotics and Male Reproductive Health

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Lessons from the occupational arena demonstrate the potential of industrial chemicals to damage human testicular function. An important but still unresolved question is whether low-level xenobiotic exposure of the general population poses a hazard. In this volume of the *Asian Journal of Andrology*, this issue is addressed by a series of reviews on xenobiotic exposure profiles, possible biological mechanisms, research methods and knowledge on impact of specific exposures. Interdisciplinary research fields as gene-environment interaction and male-mediated developmental toxicity is also addressed. Papers are cross-linked by answers to questions mutually put forward by the authors.

Several undisputed lessons from the past demonstrate how xenobiotics in the environment may have profound impact on male reproductive health. The most known cases are from the occupational arena and following environmental disasters. More than 30 years ago it was almost concomitantly reported from the United States and from Israel that the nematocide dibromochloropropane (DBCP) causes severely reduced sperm counts and even sterility in workers manufacturing or applying this pesticide (1,2). Since this discovery numerous occupational semen studies have provided considerable although less compelling evidence that some heavy metals, some halogenated organic solvents, some fungicides and other compounds are male reproductive toxicants (3). Following the Seveso disaster in northern Italy in 1976 a remarkable increase in the proportion of girls was reported among offspring of heavily

dioxin exposed men (4). Thus the overarching question is not whether environmental chemicals may represent a hazard to male reproductive health, but how important this hazard at exposure levels found in the general population is in comparison with other risk factors and causes.

Alarming reports from the 80's and 90's including the Danish 1992 report on a global major decline in sperm counts (5) have fuelled speculations that the environmental impact may be substantial because only changing environmental factors can explain dramatic changes in health outcomes across short time period. With one notable exception, testicular cancer, there is, however, no scientific consensus that sperm counts and various testicular disorders have changed markedly over past 50-100 years (6,7), and some researchers doubt that there ever will be provided valid data to corroborate or refute alleged changes in male reproductive health (8). The only long-term prospective study of semen quality with repeated yearly examinations in Denmark do not indicate that changes of sperm count has taken place during past 15 years (9). There is more reliable, but yet limited evidence indicating regional differences in sperm counts (10,11) but other comparative studies of semen quality have shown remarkable similar sperm count distributions in different regions including remote populations (12,13).

In this special issue of the *Asian Journal of Andrology* the environmental xenobiotic impact on male reproductive health is highlighted through a series of invited papers by authors who have advanced knowledge in this field during past 20-30 years. First thing to notice is the current strong evidence that not only workers in specific occupations, but the general population worldwide is exposed above natural background levels to hundreds of chemicals that have been released into the environment - in particular during the last half of the 20th century (14). Some of these chemicals are biopersistent and are eliminated at an extremely slow rate in spite of a total worldwide ban of production and use several years ago. There has been a great development in epidemiological and laboratory methods to perform observational studies in humans – in particular with respect to functional measures of fertility and laboratory refinements of studies of semen quality (15, 16). We have also seen developments in

understanding of the mechanisms by which environmental xenobiotics may impact on male reproductive function. Processes related to oxidative stress at the cellular level may be an important mechanism explaining loss of fertilising capacity of spermatozoa (17). But although it is well-established that some chemicals may produce oxidative stress in the male reproductive tract and in spermatozoa, it is still unknown whether exposures to occupational and environmental man-made chemicals are doing harm through such mechanisms. Tobacco smoking is a very strong inducer of oxidative stress in the organism and effects on sperm structure and function may be mediated thorough this mechanism in the adult as well as the fetal male gonad (18, 19).

Endocrine disruption is another mechanistic pathway that has received considerable attention. It is beyond any doubt that sexual hormones are playing a profound role for proper development and functioning of male reproductive capability. During past 20 years it has become evident that numerous chemicals in our environment may interfere with endogenous hormone signalling or by themselves act as hormones by interference with steroid hormone receptors. Therefore it seems reasonable to speculate that disruption of endocrine pathways is an important mechanism by which xenobiotics can interfere with male reproductive function, *in-vitro* and animal studies being of great importance for clarifying the mechanistic aspects of such effects (20, 21). There is evidence that high occupational exposure and extreme environmental exposure to the anti-androgenic dichlorodiphenyltrichloroethane (DDT) metabolite dichlorodiphenyldichloroethylene (DDE) reduces sperm counts in adult males. However, the evidence on adverse effects of low-level exposure to biopersistent compounds as organo-chlorines and rapidly metabolized compounds as phthalates is conflicting. So far no clear picture of the magnitude of impact of these compounds in the general population (if any) has emerged (22). Similarly, there is strong experimental evidence of developmental toxicity mediated through exposure of male gametes (23), but still the importance of environmental xenobiotic exposure is very scarce, perhaps except the convincing data indicating increased risk of congenital malformations in offspring of male smokers (Anderson D et al AJA 2013).

In any case, it is too early to conclude that concerns about major impact of male reproductive health from environmental chemicals has been exaggerated, because studies addressing risk related to early exposures in fetal life and childhood are still almost missing. This major research gap needs to be remedied and the development of large mother child cohort with biobanked blood specimens provides hope that this gap in knowledge will be filled in within a foreseeable future. Moreover, interdisciplinary research collaboration which enables large studies of gene-environment interactions may prove an important tool to distinguish random from genuine biological associations and for identifying sub-populations with increased sensitivity to the adverse effect of environmental chemicals (24).

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