

Bisphenol A exposure and sexual dysfunction in men

Editorial commentary on the article ‘Occupational exposure to bisphenol-A (BPA) and the risk of self-reported male sexual dysfunction’ Li *et al.*, 2009.

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There is a long, ongoing controversy about the potential health effects of bisphenol A in humans (Bucher *et al.*, 2009*). There are two, diametrically opposed views. One side argues vociferously, based on animal experiments, that bisphenol A may exert numerous adverse effects in humans, ranging from reproductive development disorders through obesity effects to cancer induction/progression. The other side argues, also based on animal experiments, that bisphenol A poses no significant health risks to humans. This stand-off is not simply about ‘scientists squabbling about who is right or wrong’, as there are similar differences in reaction between authorities, as Canada and some US states have chosen to ban use of bisphenol A in baby feeding bottles, whereas others (e.g. EU) have said there is nothing for consumers to worry about. What is not disputed is that we are all exposed daily to bisphenol A (Calafat *et al.*, 2008*); our exposure is mainly via bisphenol A that has leached into food from containers (Kang *et al.*, 2006*), as it is used in the making of (heat-resistant) polycarbonate plastics that are used widely as containers for food and beverages as well as in tin-can linings. As with all ‘environmental’ chemicals, the question is whether our exposure is sufficient to cause adverse health effects. Based on the same evidence, different scientists and different authorities appear to have deciphered a very different answer to this question (Bucher *et al.*, 2009*), so the non-involved outsider has every reason to be confused.

What has been largely lacking until recently has been any evidence from human studies to support the viewpoints of either of the ‘camps’. One large study in 2008 does produce evidence of an association between urinary levels of bisphenol A and occurrence of diabetes and abnormal liver function in adults (Lang *et al.*, 2008*). However, even this association could be fortuitous because bisphenol A levels could simply be a reflection of lifestyle; those with higher levels of bisphenol A being those who consume most soft drinks (Kang *et al.*, 2006*; Carwhile *et al.*, 2009*), and thus sugar, and it is this that leads to the disorders (as we know it can do in the long term). A new study in the present issue of *Human Reproduction* shows that occupationally high exposure of men to bisphenol A is associated with a dramatic increase in occurrence of sexual dysfunction (Li *et al.*, 2009*). Does this mean that, finally, the controversy over bisphenol A effects is resolved and that we (and especially us men) should be concerned about whether our bisphenol A exposure is affecting our sexual wellbeing? As outlined below, answering this question is not straightforward and in many respects the new study simply resurrects issues about the disputed actions of bisphenol A that have never been satisfactorily resolved. These now need to be answered if we are to make the correct, informed decision over how concerned to be about these new findings.

The study by Li *et al.* (2009)* shows that men who are occupationally exposed to bisphenol A have a ~4- to 7-fold increased chance of exhibiting sexual dysfunction (depending on the measure of dysfunction used), compared with men working in jobs that do not involve bisphenol A exposure. By epidemiological standards, these are large and highly significant changes. Indeed, when the authors looked at changes in sexual function in men who had

moved from a job that did not involve exposure to bisphenol A to one that did, the odds of their sexual function deteriorating were increased 6- to ~18-fold. On the face of it these findings are alarming, the more so for hitting men in their psychologically most sensitive regions. At its most sensational, the findings could mean that our exposure to bisphenol A from drinks and food containers could impair male sex drive and performance. However, this appears highly unlikely. In the men who were occupationally exposed, their urinary bisphenol A levels were more than 50-fold higher than in the men who were not occupationally exposed (the controls), and it is the latter who represent the normal population, which hopefully includes you and me. Virtually all men are exposed to varying levels of bisphenol A, but in >95% their levels of exposure remain at least 10-fold lower (Calafat *et al.*, 2008*) than the average levels of exposure shown to occur occupationally in the study by Li *et al.* (2009)*.

Despite this reassurance, the results do raise concerns. For example, babies in neonatal intensive care are exposed to 10-fold higher than normal levels of bisphenol A (Calafat *et al.*, 2009*) and children are up to 2-fold more exposed in general than are adults (Calafat *et al.*, 2008*). Sexual dysfunction is not of concern to these age groups, but could there be other effects on the developing brain or reproductive system? The answer to this probably depends on which bisphenol A ‘camp’ you belong to, but to really answer the question, we need to know how bisphenol A exerts its effects, and this is where the waters get murky.

Bisphenol A is a weak estrogen agonist that can bind to estrogen receptors (ERs) and activate a response—this has been widely suggested as the source of its (disputed) ‘adverse’ effects in (some) animal studies. However, this has always been a hard explanation to swallow, as bisphenol A is many thousand times less potent than estradiol and, as it is metabolized and excreted fast (Carwhile *et al.*, 2009*), it has always seemed to be a scientifically illogical explanation for either animal or human effects. Therefore increased estrogenic exposure due to bisphenol A seems an unlikely explanation for the sexual dysfunction found in adult men in the study by Li *et al.* (2009)*.

In men, sexual dysfunction is classically associated with androgen deficiency although depression and other factors (e.g. diabetes) can also have effects. Some studies have shown that bisphenol A is anti-androgenic and can bind to the androgen receptor (AR) and block it (e.g. Sun *et al.*, 2006*). However, all such studies have been *in vitro* and have used cells transfected with the AR (i.e. an artificial system) and evidence for similar anti-androgenic effects *in vivo* in animal studies is either sparse or lacking altogether, especially from the most detailed studies (Kobayashi *et al.*, 2002; Tyl *et al.*, 2002*; Howdeshell *et al.*, 2008*).

Moreover, even if we accept the possibility of bisphenol A having AR antagonist activity *in vivo* in man, its anti-androgenic potency is so weak that its actions via AR cannot provide a logical mechanistic explanation for the findings of Li *et al.* (2009)*, just as with its potential estrogenic effects. So there is a fundamental lack of plausibility in the idea that bisphenol A can cause effects *in vivo* at environmentally relevant levels via any mechanism that is classically AR or ER mediated. So what mechanism could underlie the apparent effects of bisphenol A on sexual function in men in the study by Li *et al.* (2009)*, and how might it affect androgen action if not through ARs (or ERs)? Non-genomic effects of androgens and estrogens are reported, if still poorly understood, and there is good evidence from *in vitro* studies that bisphenol A could work through such a mechanism. For example, one study using human adipose tissue explants or adipocytes showed that both bisphenol A (at environmentally relevant levels) and estradiol inhibited adiponectin release at equimolar levels through a mechanism that did not appear to involve ERs (Hugo *et al.*, 2008*). Some studies have suggested that bisphenol A might exert its (estrogenic) effects via the G-protein

coupled membrane receptor Gpr30, but if this is the case it is unlikely to be straightforward, as several groups have shown that knockout of Gpr30 is without significant reproductive effects (e.g. Otto *et al.*, 2009*).

Numerous studies have investigated if perinatal exposure of rodents to bisphenol A causes behavioural effects, but more relevant to present concerns is that (oral) exposure to bisphenol A in adult male rats has no reported effects on sexual behaviour or fertility (Ema *et al.*, 2001*; Tohei *et al.*, 2001*). However, there is one potentially relevant study (Leranth *et al.*, 2008*), in which castrate adult male rats were injected with testosterone with or without bisphenol A and the synaptogenic response to testosterone (formation of new synapses) then quantified in the medial prefrontal cortex and hippocampus regions of the brain after 3 days of treatment. Lesions of the prefrontal cortex in humans have negative effects on sexual behaviour/interest, possibly related to increased apathy/indifference (Baird *et al.*, 2006*). In rats, testosterone (and estrogens) induce synaptogenesis in the medial prefrontal cortex and hippocampus but this induction does not require either ARs (MacLusky *et al.*, 2006*) or ERs, and the induction is inhibited by co-treatment with bisphenol A (Leranth *et al.*, 2008*). Although the mechanism that underlies these findings might seem at face value to provide a potential explanation for the findings by Li *et al.* (2009)*, there are several cautionary points. First, the authors used a moderately high dose (300 µg/kg/day) of bisphenol A, but more importantly they injected it subcutaneously on 3 successive days, which will considerably increase exposure when compared with the oral route (the route of exposure relevant to man) (Takahashi & Oishi, 2003*)—use of an inappropriate route of exposure in animal studies has been one of the major issues underlying the dispute over bisphenol A effects. Second, the model used (castration-induced androgen withdrawal and high dose testosterone replacement) is far removed from the normal physiological situation in men. So whether the findings by Leranth *et al.* (2008)* have any relevance to the human sexual dysfunction observations of Li *et al.* (2009)* is doubtful.

The study by Li *et al.* (2009)* is likely to be overblown by some sections of the media or others, when what is really needed is a level head to evaluate the concerns that this study raise. The first thing needed is repetition of the study—if it is not repeatable (as with many previous studies with bisphenol A) then we should not accept it. This is not to cast doubt on the authors or their study, it is simply the golden first rule in science. In the meantime, we should not lose sight of the fact that even the majority (~80%) of the men occupationally exposed to bisphenol A in Li *et al.* (2009)* did not exhibit sexual dysfunction. Nor for the moment should we exclude the possibility that something else, common to the workplaces in which bisphenol A is manufactured, could be responsible for the observed effects on sexual dysfunction in men who work there. We may joke about men's one-track minds but, even in men, sexual behaviour is a highly complex process that can be affected by numerous societal and personal factors, and it can be difficult to allow for all such factors in epidemiological studies. Moreover, these factors are difficult or impossible to model in animal studies, so taking the studies by Li *et al.* (2009)* further with regard to mechanisms may be less than straightforward. However, if nothing else these new findings may finally force us to resolve the numerous uncertainties that have dogged bisphenol A research. In doing so, not only must we adhere to the accepted principles of scientific enquiry (e.g. studies must be repeatable), but 'conspiracy theory' and emotion must be left out of the debate.

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