Institution: The University of Edinburgh

Unit of Assessment: 1

Title of case study: P: Testicular Dysgenesis Syndrome is linked to endocrine-disrupting phthalate exposure; specific phthalates are now banned from children's mouth toys

1. Summary of the impact (indicative maximum 100 words)

Impact: Health and welfare; policy; the environment; fundamental changes to phthalate use, wider EU and US Endocrine Disrupting Chemical (EDC) regulations and chemical bans.

Significance: Shaped policy, regulation and the potential causal relationship of environmental EDC on male reproductive disorders and testicular dysgenesis syndrome.

Beneficiaries: Governments; chemical and food regulatory agencies; healthcare workers advising and treating pregnant women; pregnant women and their fetuses; males with disorders of sex development; adult males; plastics manufacturers.

Attribution: EDC research was developed and shaped by Prof Richard Sharpe and colleagues at UoE.

Reach: International; Europe, North America.

2. Underpinning research (indicative maximum 500 words)

Led by Professor Richard Sharpe (Programme Leader and Principal Investigator, MRC Centre for Reproductive Health, UoE, 1974–present), UoE-based researchers played the key role in demonstrating that the widely used plasticiser, dibutyl phthalate (DBP) was a cause of testicular dysgenesis syndrome (TDS) by suppressing androgen production. This finding had critical implications for the framing of environmental and chemical legislation in Europe and North America, and for the manufacture and sales of children's toys and products that might be "mouthed".

Sharpe played the key role in generating the so-called 'oestrogen hypothesis' (1993) [3.1] (>1800 citations), [3.2] (>1300 citations). This created worldwide interest, concern and controversy by interlinking the high or rising incidence of human male reproductive disorders (collectively termed 'testicular dysgenesis syndrome', TDS) with increased exposure to environmental oestrogens via environmental chemicals or diet [3.3]. Work at UoE between 2005 and 2008 identified that only potent (pharmaceutical, not environmental) oestrogens induced male reproductive disorders by suppressing androgen production or action, reducing expression of androgen receptor protein [3.4]. This led to a refocusing on fetal androgens and their perturbation; in particular, the potential role that exposure to anti-androgenic endocrine-disrupting chemicals (EDC) might play. Sharpe and others identified that certain phthalate esters (widely used to enhance the malleability of plastic components, objects and toys), to which there is ubiquitous human exposure, can suppress androgen production by the fetal rat testis. The next key development in the field was the development and validation by Sharpe's group of animal models of TDS, based on exposure of pregnant rats to one of these compounds, dibutyl phthalate (DBP) [3.5]. This work has been instrumental in validating the TDS hypothesis (which was untestable in man), and in identifying both the interlinking of TDS and its common mechanistic origins in fetal life, which can then be applied in man. The wide use of phthalates in the manufacture of plastics encompasses a range of products, including those to which pregnant females, neonates and babies are frequently exposed. Sharpe and colleagues' research has played a lead role in risk assessment and regulation of the relevant phthalates, and in shaping worldwide research on these compounds.

The models developed by UoE investigators for the first time allowed (a) retrospective determination of the origin in fetal life, and causes, of TDS in humans, in particular those emerging

in young adulthood such as low sperm count or testis germ cell cancer, (b) the identification of the 'masculinisation programming window' (MPW; ~8–12 weeks' gestation in humans): the critical fetal period when function, reproductive organ size and reproductive disorders in newborn and adult males are predetermined by the level of androgen exposure, and (c) determination that anogenital distance (AGD), which is sexually dimorphic, was also programmed by androgen exposure in the MPW, and could be used from birth to adulthood to determine fetal androgen exposure in the MPW retrospectively [3.6]. This had major consequences: (i) it identified a critical window: EDC could only induce TDS if maternal (fetal) exposure occurred during the MPW; (ii) it allowed the application of AGD measurement in humans as a means to retrospectively determine the origin of TDS, and/or to forecast future reproductive function or disorders in adults, and/or at birth to identify directly potential causal association between EDC exposure and reproductive development; and (iii) it provided a biomarker for regulatory purposes [3.6].

3. References to the research (indicative maximum of six references)

3.1 Sharpe R, Skakkebaek N. Are oestrogens involved in falling sperm counts and disorders of the male reproductive tract? Lancet. 1993;341:1392–5. DOI: 10.1016/0140-6736(93)90953-E.

3.2 Toppari J, Larsen J,…Sharpe R, et al. Male reproductive health and environmental xenoestrogens. Environ Health Perspect. 1996;104:741–803. DOI: 10.2307/3432709.

3.3 Sharpe R. The 'oestrogen hypothesis'. Where do we stand now? Int J Androl. 2003;26:2–15. DOI: 10.1046/j.1365-2605.2003.00367.x.

3.4 Rivas A, McKinnell C, Fisher J, Atanassova N, Williams K, Sharpe R. Neonatal co-administration of testosterone with diethylstilbestrol prevents diethylstilbestrol induction of most reproductive tract abnormalities in male rats. J Androl. 2003;24:557–67. DOI: 10.1002/j.1939-4640.2003.tb02707.x.

3.5 Fisher J, Macpherson S, Marchetti N, Sharpe R. Human 'testicular dysgenesis syndrome': a possible model using in-utero exposure of the rat to dibutyl phthalate. Hum Reprod. 2003;18:1383–94. DOI: 10.1093/humrep/deg273.

3.6 Welsh M, Saunders P, Fisken M,…Sharpe R. Identification in rats of a programming window for reproductive tract masculinization, disruption of which leads to hypospadias and cryptorchidism. J Clin Invest. 2008;118:1479–90. DOI: 10.1172/JCI34241.

4. Details of the impact (indicative maximum 750 words)

Pathways to impact

Expert advice underpinning legislative changes in both Europe and North America leaned heavily on Sharpe's work. Sharpe has contributed to expert reports to policy-makers at the highest levels. Examples include: the Advisory Committee on Hazardous Substances (2010); the European Parliament Science and Technology Options Assessment (2013); the European Science Foundation (2010); the European Environment Agency [5.1]; the US National Academies Committee on Health Risks of Phthalates (2008); the US Consumer Product Safety Commission: US Chronic Hazard Advisory Panel on Phthalates (2011); Food and Agriculture Organisation/the World Health Organization (2012) [5.2]; EC Scientific Committee on emerging and newly identified health risks (2013); and the US Department of Health & Human Services National Toxicology Program (2008). Invitations to speak at critical European and international conferences included: the European Chemical Industry on EDC and phthalates, ECETOC (2009), European (2012) and International (2013) Plasticizers conferences, and a critical review for the NGO ChemTrust (2009) on the role of EDC in TDS [5.3]. Sharpe has also acted as expert adviser to many companies, including Johnson & Johnson (2009; safety of phthalates in children's toys), Bayer (2013), and BASF (2011–13; scientific advisory panel).

Impact on public policy

Sharpe's research at UoE, with others (such as Swan's group in the USA) fundamentally altered UK and EU and significantly influenced North American attitudes to EDC in general, and to phthalates specifically, their presence in the environment and their associated potential health

effects, especially in high-risk groups where there is exposure to EDC at critical periods in development or susceptibility: in utero and in childhood.

Sharpe's work on the impact of environmental exposure to EDC and phthalates alerted legislators to the developmental dangers of EDC exposure and took a lead role in driving a radical reformulation of regulations for the manufacture and use of all chemicals in Europe: REACH (Registration, Evaluation, Authorisation & Restriction of Chemicals) [5.4, 5.5]. REACH represented a critical shift in liability, placing the onus on chemical manufacturers to prove the safety of their compounds before approval and registration. It also encompassed retrospective evaluation of key chemicals where manufacture and use preceded REACH implementation (in particular EDC), and laid the foundations for new regulation of EDC in food by the European Food Safety Authority [5.6].

Sharpe's work linking TDS to phthalate exposure led to certain phthalates being banned from use in children's toys and childcare articles [5.7–5.10], as detailed below.

Following an EC Recommendation on the ban of phthalates in children's toys in 1998, eight member states (Austria, Denmark, Finland, France, Germany, Greece, Italy and Sweden) restricted the use of phthalates in toys and in childcare articles, with the other member states taking a 'controlled use' approach by measuring the release of phthalates from children's toys. In 1999 the EC published a "Community Strategy for Endocrine Disruptors" followed (to 2011) by a series of official reports dealing with its implementation [5.1, 5.7].

Subsequently, the EU Phthalates Directive 2005/84/EC banned the use of certain phthalates (DEHP, DBP and BBP) in PVC and other plasticised materials in all toys and childcare articles throughout the EU from January 2007. Phthalates DINP, DIDP and DNOP were banned for toys and childcare articles that could be placed in the mouth of children of all ages, even if in parts unlikely to be mouthed [5.8]. The impact extends further than children's articles: since 2010, Denmark's Environmental Protection Agency has put pressure on the EU to ban phthalates from sex toys with new restrictions in REACH planned by the European Chemicals Agency.

The impact of Sharpe's research on EU policy and legislation is referred to by the primary EU website on this area of healthcare, the Endocrine Disruptors Website [5.7]. EU strategy for short, medium and long-term actions on EDC management in the EU is covered; Sharpe's research is referenced several times in its supporting database.

In 2009, the US Congress banned six phthalates from children's toys throughout the USA; additional requirements added in 2011 require third-party testing and certification for products manufactured after 31 December 2011 [5.9]. A CBS in-depth video article (May 2010) quoted Sharpe and acknowledged that "Dr. Sharpe's study led to Congress banning the phthalates in toys" [5.10]. In Canada, the same six phthalates were banned from all children's toys and childcare articles in 2011.

5. Sources to corroborate the impact (indicative maximum of 10 references)

5.1 European Environment Agency (EEA) report: The impacts of endocrine disrupters on wildlife, people and their environments. 2012. EEA technical report No 2/2012; ISSN 1725-2237. http://www.pnrpe.fr/IMG/pdf/Tech_02_2012_1_-2.pdf.

5.2 Joint FAO/WHO Expert Meeting to Review Toxicology and Health Aspects of Bisphenol A. 2010. ftp://ftp.fao.org/ag/agn/agns/BPA_Summary_Report.pdf.

5.3 ChemTrust Joint NGO Press Release on EFSA's Opinion on BPA (Bisphenol A) http://www.chemtrust.org.uk/Press_and_Media.php.

5.4 Health and Safety Executive REACH homepage. http://www.hse.gov.uk/reach/.

5.5 European Chemicals Agency Regulations: REACH http://echa.europa.eu/web/guest/regulations/reach.

5.6 EFSA Paves Way for Regulating Endocrine Disruptors in Food.2013. http://www.euractiv.com/health/food-safety-agency-backs-definin-news-518638.

5.7 EC Endocrine Disruptors homepage. http://ec.europa.eu/environment/endocrine.

5.8 EU Phthalates Directive 2005/84/EC Update. 2006. http://www.intertek.com/uploadedFiles/Intertek/Divisions/Consumer_Goods/Media/PDFs/Sparkles/2006/sparkle250.pdf.

5.9 United States Consumer Product Safety Commission website. http://www.cpsc.gov/phthalates.

5.10 Phthalates are they safe? 2010. CBS 60 mins video http://www.cbs.com/shows/60_minutes/video/1500260381/phthalates-are-they-safe.