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Supplemental Material

Proposed Key Characteristics of Male Reproductive Toxicants as an Approach for Organizing and Evaluating Mechanistic Evidence in Human Health Hazard Assessments

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Table S1: Endpoints considered for hazard evaluation of chemical-induced male reproductive effect

Male-specific endpoints of reproductive toxicity[1]	
Male-specific endpoints of reproductive toxicity	***Description***
Visual examination and histopathology	Testes, epididymis, seminal vesicles, prostate, pituitary. E.g. in the testis: Sertoli cell only tubules, seminiferous tubule vacuolation, etc. (U.S.EPA, 1996; Creasy et al., 2012; Woldemeskel, 2017).
Gross pathology	E.g. absent, small or fluid filled testes, absent, small or infected ventral prostate, dorsolateral prostate, and epididymis, etc. (Foster and Gray, 2013).
Sperm evaluation*	Alterations in sperm production, number (count) and quality (morphology, motility) (U.S.EPA, 1996; Klinefelter, 2015). Evaluation of functional activity: hyperactivated motility, capacitation/acrosome reaction tests, sperm penetration assay, sperm DNA integrity test (WHO, 2010; Sikka and Hellstrom, 2016; Creasy and Chapin, 2018).
Developmental effects (i.e. disrupts morphogenesis; promotes structural disorganization)*	Testis descent (i.e. cryptorchidism)*, absent/small/fluid filled/enlarged testis, preputial separation, sperm production*, anogenital distance*, areola/nipple retention, structure of external genitalia (e.g. hypospadias, epispadias, cleft phallus)*, reproductive organ size/development (e.g. small or absent testes, epididymis, prostate, seminal vesicle and coagulating glands (U.S.EPA, 1996; WHO, 2006; Skakkebaek et al., 2016; Thankamony et al., 2016; Creasy and Chapin, 2018).
Hormone levels*	Disruption of production/secretion of gonadotropin releasing hormone, Luteinizing hormone, follicle stimulating hormone, testosterone, INSL3, inhibin (U.S.EPA, 1996; Chapin and Creasy, 2012; Schrader and Marlow, 2014).
Sexual behavior/functions*	Erection, time periods to first mount, mount with intromission, and first ejaculation, number of mounts with intromission to ejaculation, and the postejaculatory interval (U.S.EPA, 1996; Foster and Gray, 2013).
Organ weights	Testes, epididymis, seminal vesicles, prostate, adrenals, levator ani plus bulbocavernosus, glans penis, pituitary (U.S.EPA, 1996; Sellers et al., 2007; Creasy and Chapin, 2018).
*Reproductive endpoints that can be obtained or estimated relatively noninvasively with humans.	

Sexual behavior may be disrupted via alterations in endocrine, neural, and reproductive organ interactions. Outcomes that are considered indicative of adverse responses in the male reproductive system "include latency periods to first mount, mount with intromission, and first ejaculation, number of mounts with intromission to ejaculation, and the post ejaculatory interval" (U.S.EPA, 1996). These types of responses are considered adverse during a hazard evaluation (U.S.EPA, 1996).

[1] Adapted from U.S.EPA, 1996. Guidelines for reproductive toxicity risk assessment. U.S. Environmental Protection Agency; Risk Assessment Forum, Washington, DC, pp. 25-34.

Table S2: Example Key Terms Relevant for Identifying Evidence on Chemical-Induced Male reproductive Toxicity

"male reproductive"[Title/Abstract] OR "reproductive development" [Title/Abstract] OR "endocrine disruptors"[Title/Abstract] OR "environmental chemicals"[Title/Abstract] OR pharmaceuticals[Title/Abstract] OR pesticides[Title/Abstract] OR spermatogenesis[Title/Abstract] OR "Leydig cells"[Title/Abstract] OR "Sertoli cells"[Title/Abstract] OR "germ cells"[Title/Abstract] OR spermatozoa[Title/Abstract] OR testis[Title/Abstract] OR "environmental factors"[Title/Abstract] OR infertility[Title/Abstract] OR sperm[Title/Abstract] OR epididymis[Title/Abstract] OR "hypothalamic-pituitary-gonadal axis"[Title/Abstract] OR "cell signaling"[Title/Abstract] OR androgen[Title/Abstract] OR estrogens[Title/Abstract]) OR Anogenital[Title/Abstract] OR "AGD" [Title/Abstract] OR Azoospermia[Title/Abstract] OR Ejaculation[Title/Abstract] OR "ejaculatory duct" [Title/Abstract] OR Epididymis[Title/Abstract] OR Penis[Title/Abstract] OR "Seminiferous tubules" [Title/Abstract] OR "Sex differentiation" [Title/Abstract] OR "Sexual development" [Title/Abstract] OR Testosterone[MeSH:NoExp] OR "Prenatal Exposure Delayed effects"[MeSH] OR "Environmental Exposure"[MeSH:NoExp] OR "Maternal Exposure"[MeSH] OR "Genital Diseases, male"[MeSH] OR "Genitalia, Male"[MeSH] OR Androgens[MeSH]

The development of a literature search strategy is a key step in the systematic review process. Identifying the key terms that will bring together the body of literature that will be analyzed requires a thoughtful and deliberate search strategy. Systematic reviews typically require the search of multiple databases to capture all studies relevant to the specific research question, and search strategies must be customized to each database. As such, the terms listed above represent key terms that would be relevant when addressing a research question with male toxicity as an outcome of interest. This example list for literature search key terms does not represent an exhaustive search strategy but can provide a starting point for further defining and customizing the strategy specific to the criteria for the systematic review question. In addition, MeSH (Medical Subject Headings), an indexing feature from the National Library of Medicine's controlled vocabulary thesaurus, can be used to retrieve relevant sources in MEDLINE/PubMED.

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