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February 16, 2016

Chairman Elliot Kaye (via e-mail: EKaye@cpsc.gov)
U.S. Consumer Product Safety Commission
4330 East West Highway
Bethesda, MD 20814

Dear Chairman Kaye,

Please find attached a copy of a letter sent from Dr. Jennifer Foreman, a toxicologist at ExxonMobil Biomedical Sciences Inc. (EMBSI), to CPSC Assistant Executive Director for Hazard Identification and Reduction Dr. George Borlase. The letter summarizes preliminary conclusions of the EPA Integrated Risk Information System (IRIS) Assessment Manager for Dibutyl Phthalate (DBP), Dr. Xavier Arzuaga, from his review of DBP anti-androgenicity data, as he presented at two scientific meetings in December 2015. Dr. Foreman notes that the presentations indicate the IRIS staff is concluding that laboratory rats are particularly sensitive to the anti-androgenic effects of DBP on the developing fetus. The increased sensitivity of rats to those effects has important implications for human health assessments.

This is noteworthy because the cumulative risk assessment conducted by both Chronic Hazard Advisory Panel (CHAP) and CPSC science staff was based on effects of phthalates including DBP on the developing rat fetus, and used these effects as the basis to calculate hazard indices. You may recall that the staff reanalysis of the CHAP data found that cumulative risk, which is a measure of both hazard and exposure, has decreased over the years based on the most recent National Health and Nutrition Examination Survey (NHANES) biomonitoring data. If the anti-androgenic effect in rats is determined to have little or no relevance for humans, then the calculated hazard indices would be even lower. This should increase the CPSC's confidence that the hazard indices are less than one, and that there is no concern regarding anti-androgenic effects in humans based on the cumulative effects of phthalates.

Dr. Foreman requested a face-to-face meeting with the CPSC science staff to share EMBSI's analysis of the cumulative risk assessment incorporating this information as well as other scientific updates. We are hopeful that this meeting will occur in the near future. In the meantime, please let me know if you would like to further discuss these findings.

Sincerely,

Cc – with attachment:
Commissioner R. Adler (RAdler@cpsc.gov)
Commissioner A. Buerkle (ABuerkle@cpsc.gov)
Commissioner J. Mohorovic (JMohorovic@cpsc.gov)
Commissioner M. Robinson (MRobinson@cpsc.gov)
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February 5, 2016

2016EMBSI 37

Dr. George Borlase (via email: GBorlase@cpsc.gov)
Associate Executive Director
Office of Hazard Identification and Reduction
U.S. Consumer Product Safety Commission (CPSC)
4330 East West Highway
Bethesda, MD 20814

Dear Dr. Borlase,

I recently attended The Society for Risk Analysis Annual Meeting in December 2015 held in Arlington, Virginia, where I listened to a presentation that may be of interest to you and your team. The presentation was given by the Integrated Risk Information System (IRIS) Assessment Manager for Dibutyl Phthalate (DBP), Xabier Arzuaga, entitled, "Application of an Adverse Outcome Pathway (AOP) framework to evaluate species concordance and human relevance of Dibutyl Phthalate (DBP)-induced toxicity to the male reproductive system". Dr. Arzuaga also gave a very similar version of this talk at the Environmental Protection Agency's (EPA) "Advancing Systematic Review Workshop" (December 2015), for which the slides are publicly available.

A link to the presentation has being provided in the e-mail accompanying this letter, and a copy of these slides is also attached for your convenience.

The key point of interest to CPSC science staff is the conclusion being drawn by EPA's IRIS staff on the human relevance of the anti-androgenic effects of DBP in-utero. Specifically, the anti-androgenic effects induced in laboratory rats by fetal exposure to DBP are decreased testosterone, external & internal malformations, decreased anogenital distance (AGD), and decreased fertility. As you know, these are the effects on which the Chronic Hazard Advisory Panel (CHAP) on Phthalates based its cumulative risk assessment and on which the recommendation to make permanent the ban on DINP was based.

EPA staff undertook a structured assessment of the same literature available to the CHAP, plus several recent publications that were not yet available to the CHAP. As indicated by the attached slides, and more pointedly indicated by Dr. Arzuaga in his presentations, EPA scientists are highlighting the unique sensitivity of this endpoint in rats, which indicates the EPA is moving away from assigning importance to the developmental anti-androgenic endpoints for purposes of human health assessment.

> Slide 13: "Fetal rats appear more sensitive to DBP-induced anti-androgenic effects than are mice and may be more sensitive than other rodent species, non-human primates, and human fetal testis xenografts and ex-vivo tissue cultures"
>
> Slide 21: "Rats appear to be more sensitive to DBP-induce anti-androgenic effects during gestation"

Under the CPSC staff reanalysis of phthalate cumulative risk, current exposure levels generated hazard indices (HIs) for the anti-androgenic effects of phthalates in-utero that were below 1 at the 95 percentile, the percentile used for the safety determination of individual phthalates by the CHAP. The analysis of the recent literature and conclusions of the EPA scientists indicate the HI values for the human population should be yet lower given the observations that rats are more sensitive to these effects.

In conclusion, the CPSC staff reanalysis indicated that the risk due to exposure was less than calculated in the CHAP report and Dr. Arzuaga's presentations indicate that the risk to humans due to the innate hazard identified (gestational anti-androgenicity) in the CHAP report is also less than originally calculated (perhaps as low as zero). Combined, these two avenues of evidence should further increase the CPSC's confidence that HIs are less than 1 and there is no concern for anti-androgenic effects in humans from the cumulative effects of phthalates.

As outlined above, the EPA staff evaluation further strengthens scientific confidence that the risk conclusions based on the cumulative risk assessment in the CHAP report are not supported by the most recent science. A decision to lift the ban on DINP, with a high level of certainty of no harm, is consistent with the science.

I am integrating the new science into our assessment to determine the degree to which the new science impacts the calculations.

We would like an opportunity to meet with you to share this new analysis. Please let us know if there is a day in February, 2016, when we can meet with your science staff to discuss how the recent literature and the EPA staff evaluation impact the calculations and conclusions for the DINP health assessment we have developed.

Sincerely,

Jennifer E. Foreman, Ph.D., DABT
Senior Toxicologist

Cc: Dr. Alice Thaler, CPSC
Dr. Michael Babich, CPSC
Dr. Ken Carlson, CPSC
Dr. Kristina Hatlelid, CPSC
Chris Wallace, ExxonMobil Chemical Company

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Examination of human relevance of anti-androgenic effects observed following exposure to dibutyl phthalate

Xabier Arzuaga PhD
U.S. EPA
Office of Research and Development
National Center for Environmental Assessment

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Objective

- Describe an ongoing project in which the Adverse Outcome Pathway (AOP) framework is being utilized to perform a systematic review of DBP-induced male reproductive effects.

The views expressed in this presentation are those of the author and do not necessarily reflect the views or policies of the U.S. EPA.

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Dibutyl phthalate (DBP)

- DBP is used as a plasticizer in resins, cellulose plastics, adhesives, solvent for dyes, and fixative for perfumes.
- The largest source of exposure to humans is food.
- DBP and other phthalates with side chain lengths between 3 and 9 carbons are known to target the male reproductive system.
- Rat studies on DBP and other phthalates suggest that early life stages (fetal and early postnatal) are the most sensitive to DBP-induced male reproductive toxicity.

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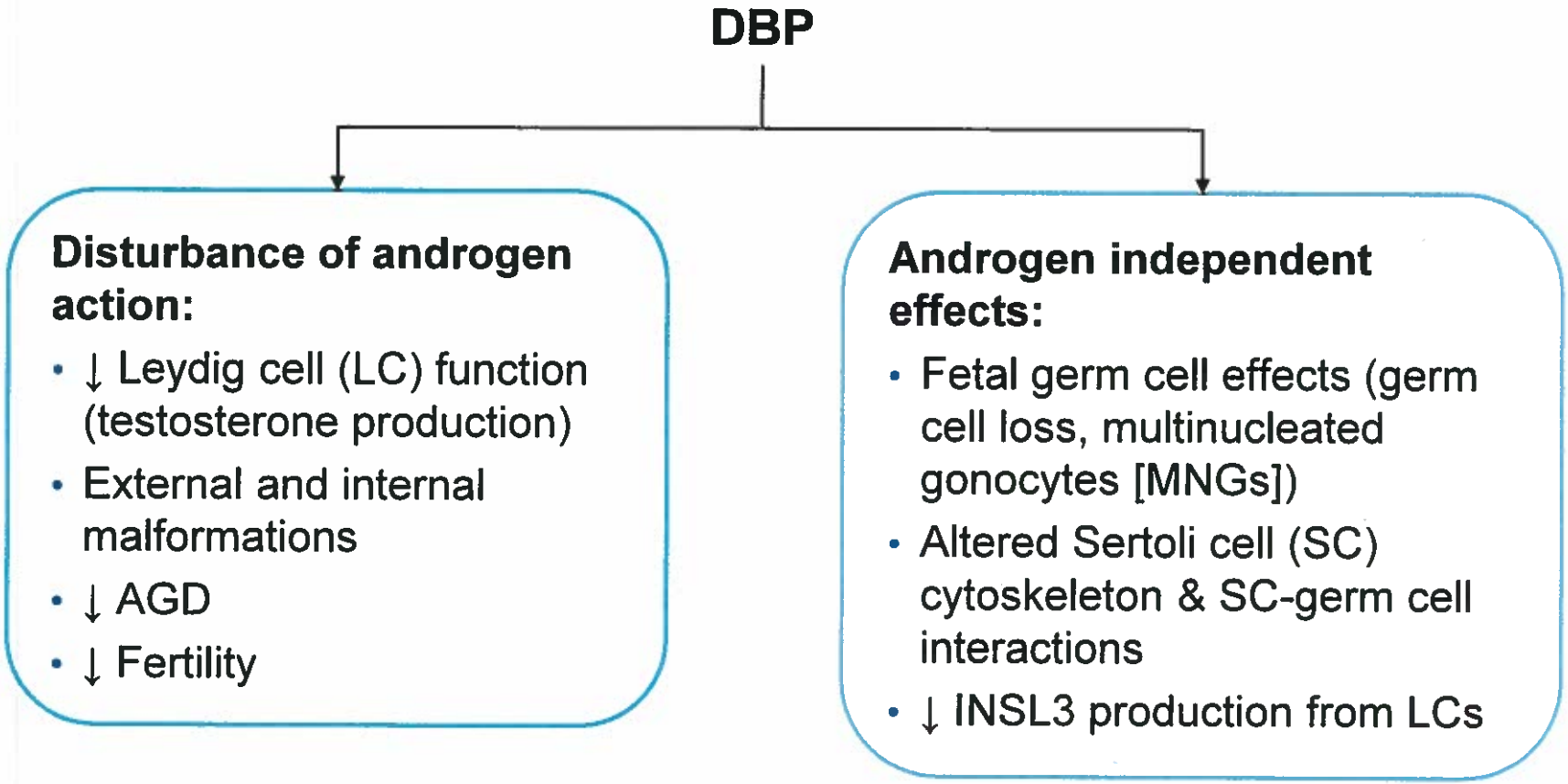
DBP-induced effects in the male reproductive system after gestational exposure



Adapted from NRC, 2008

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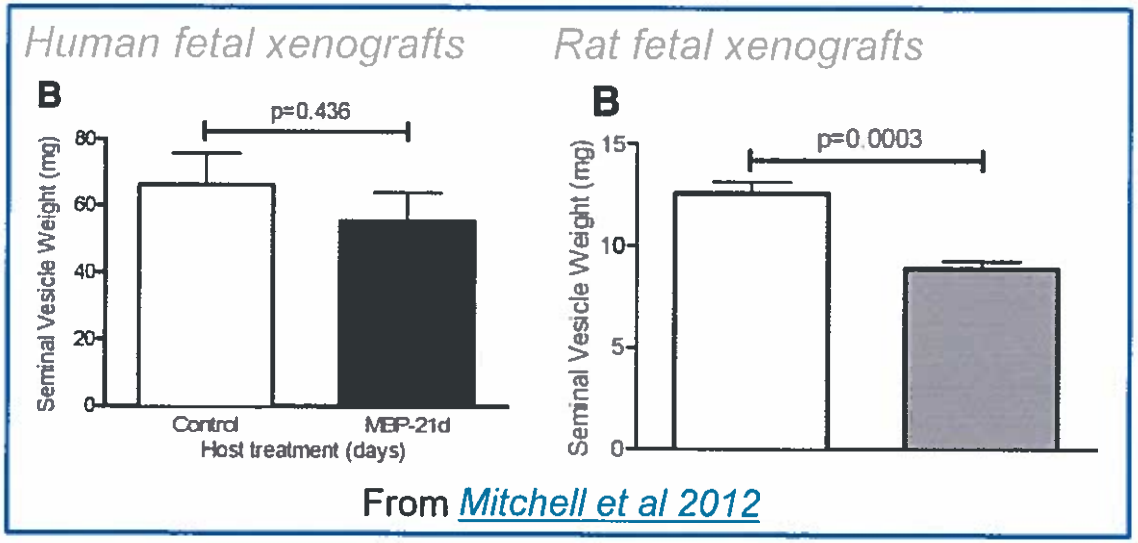
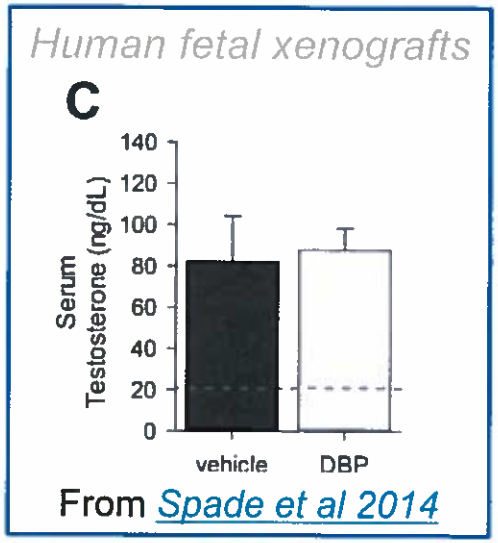
Human relevance of evidence from experimental studies

- Studies using ex-vivo human tissue culture preparations, or rodent and human testicular tissue xenografts report that human fetal testes are less sensitive to DBP-induced disruption of testosterone production (reviewed: WHO, 2012; Albert and Jégou 2014; Johnson et al 2012).



From *Mitchell et al 2012*



From *Spade et al 2014*

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Scope and objectives

- "The identification of common molecular, cellular or/and phenotypic targets in both rat and human models should precede the choice of a toxicological endpoint in the rat to accurately assess the safety threshold of any ED in humans" (Habert et al 2014).
- The AOP framework was considered to be a useful tool to integrate information from a variety of experimental models and levels of biological organization.

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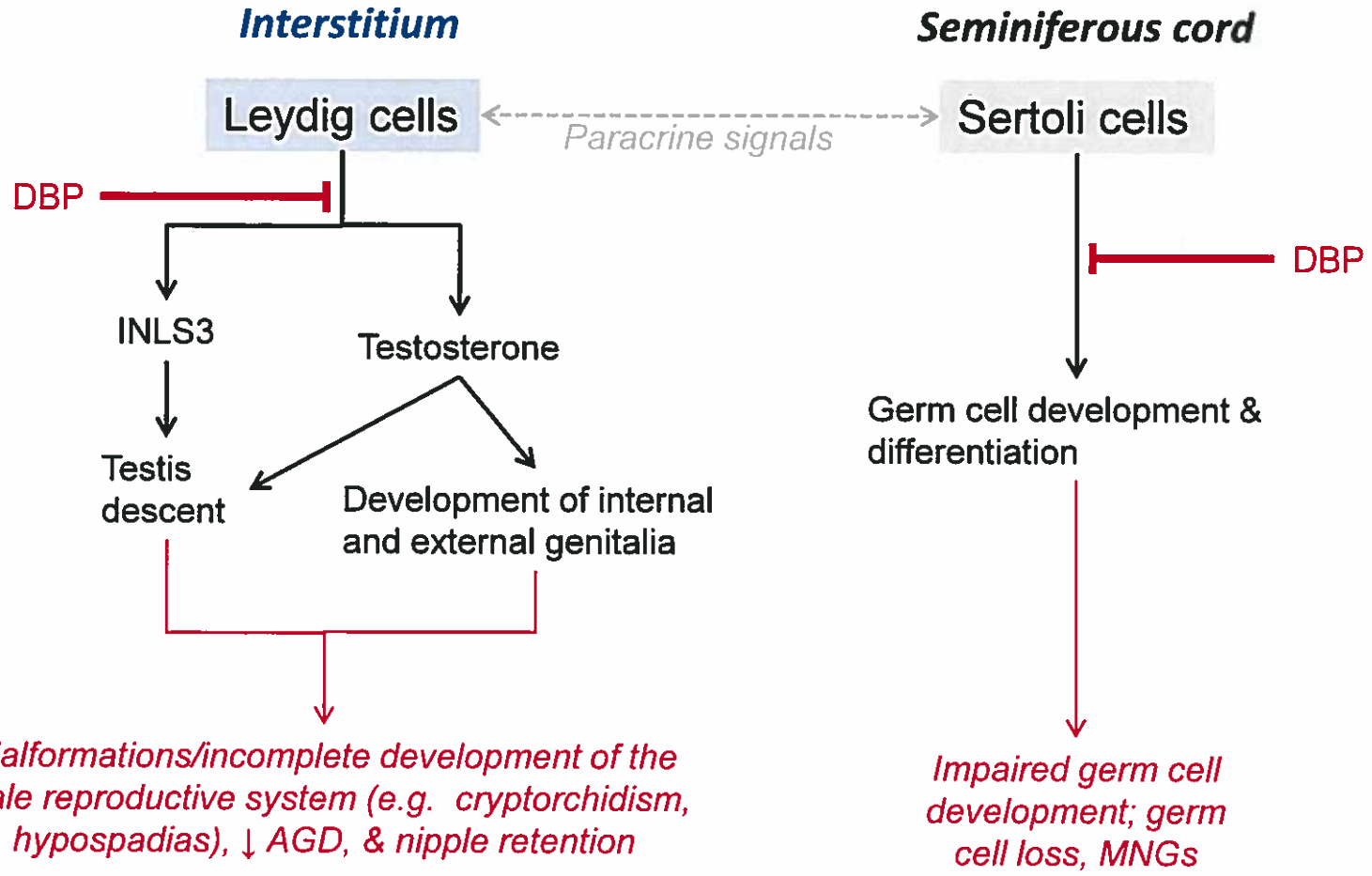
Mechanism for DBP-induced male reproductive effects (gestational exposure)



Adapted from Martino-Andrade & Chahoud 2010; Foster 2006; Sharpe & Skakkebaek, 2008; EPA 2009

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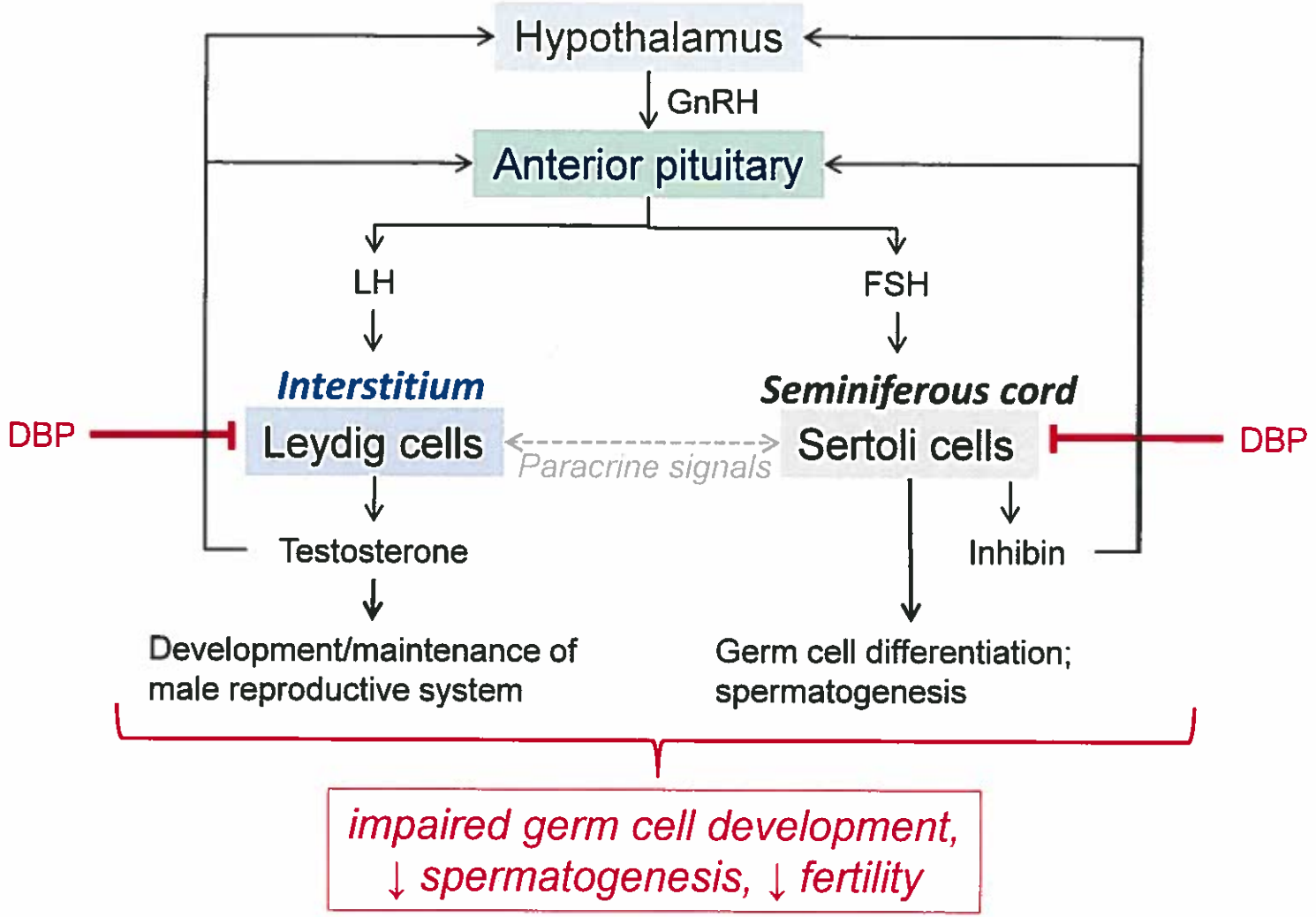
Mechanism for DBP-induced male reproductive effects (early post-natal lifestage exposure)



Adapted from: Foster and Gray 2013; Hu et al 2009

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Literature search and identification of studies

Literature search strategy developed for IRIS DBP Tox Review → Identification of toxicological and mechanistic studies → Title/abstract review (studies informative on potential reproductive effects)

Study citations and secondary literature review →

Study selection and information extraction

- **In vivo studies [~40]:** Gestation &/or post natal exposures
- **In vitro studies [10]:** Cell lines, or ex-vivo tissue culture
- **Xenograft studies [5]:** Rodent models, humans and non-human primates

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Considerations-criteria used to evaluate experimental and mechanistic evidence

- Lifestage: Due to biochemical, physiological, and endocrine differences during development, evidence was organized according to the lifestage of exposure.
  - Gestational; masculinization programming window
  - Puberty (before, during)
  - Sexually mature
- Reporting: Species and strain of animals, dosing, and exposure duration.
- Exposure route: oral, inhalation, dermal exposures, and cell culture.

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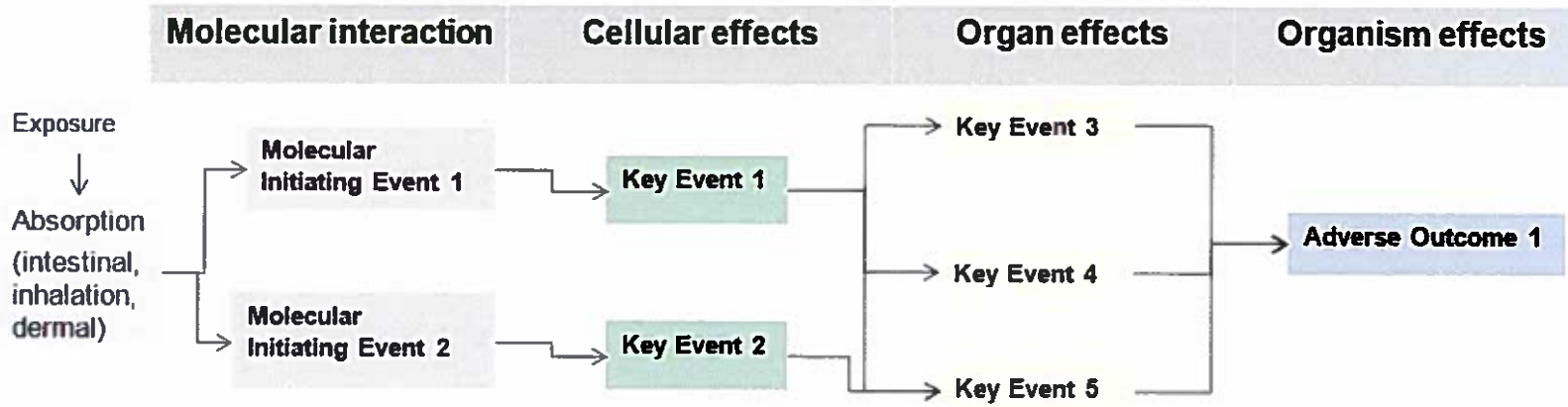
Database-inventory created for analysis of DBP-induced male reproductive effects

Study information captured in database:

- HERO ID & reference.
- Species, strain, & age/life stage of test model.
- Test compound, dose, exposure route & duration.
- Target organ categories (e.g. organ wt, hormone levels, histopathology, mechanistic, etc).
- Reported outcomes for individual effects.
- Corresponding key event or adverse outcome.

Types of experimental studies captured in database:

- In-vivo
- In-vitro (i.e. cell culture)
- Ex-vivo
- Xenograft



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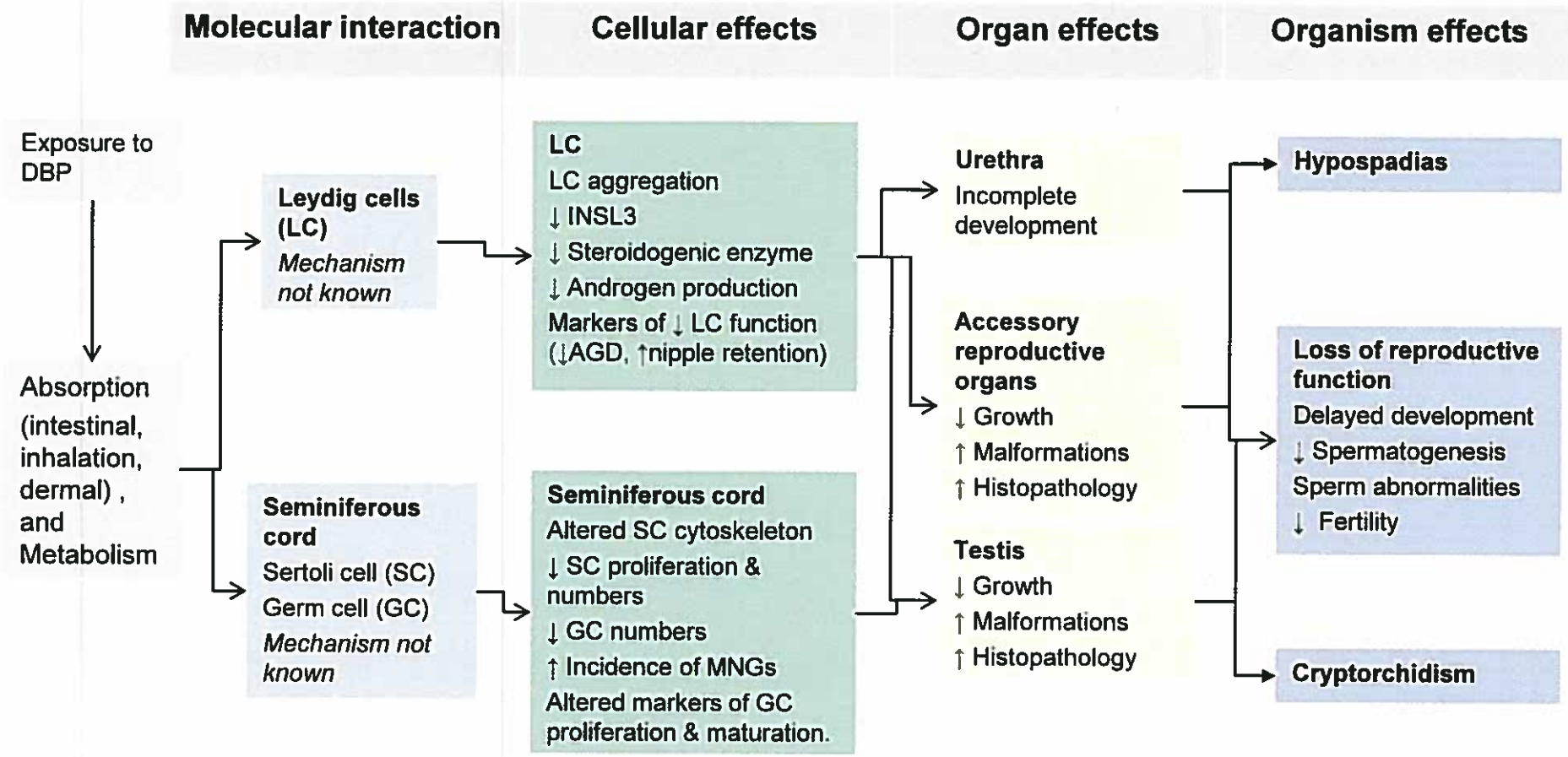
Pathway for DBP-induced male reproductive effects after gestational exposure during MPW



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Preliminary observations; gestational exposure

- Overall, the available evidence suggests that DBP exposure during gestation may alter development of the male reproductive system.
- Fetal rats appear more sensitive to DBP-induced anti-androgenic effects than are mice and may be more sensitive than other rodent species, non-human primates, and human fetal testis xenografts and ex-vivo tissue cultures.
- DBP-induced androgen-independent effects are conserved among most mammalian models (rats, rabbits and mice) and human xenografts.

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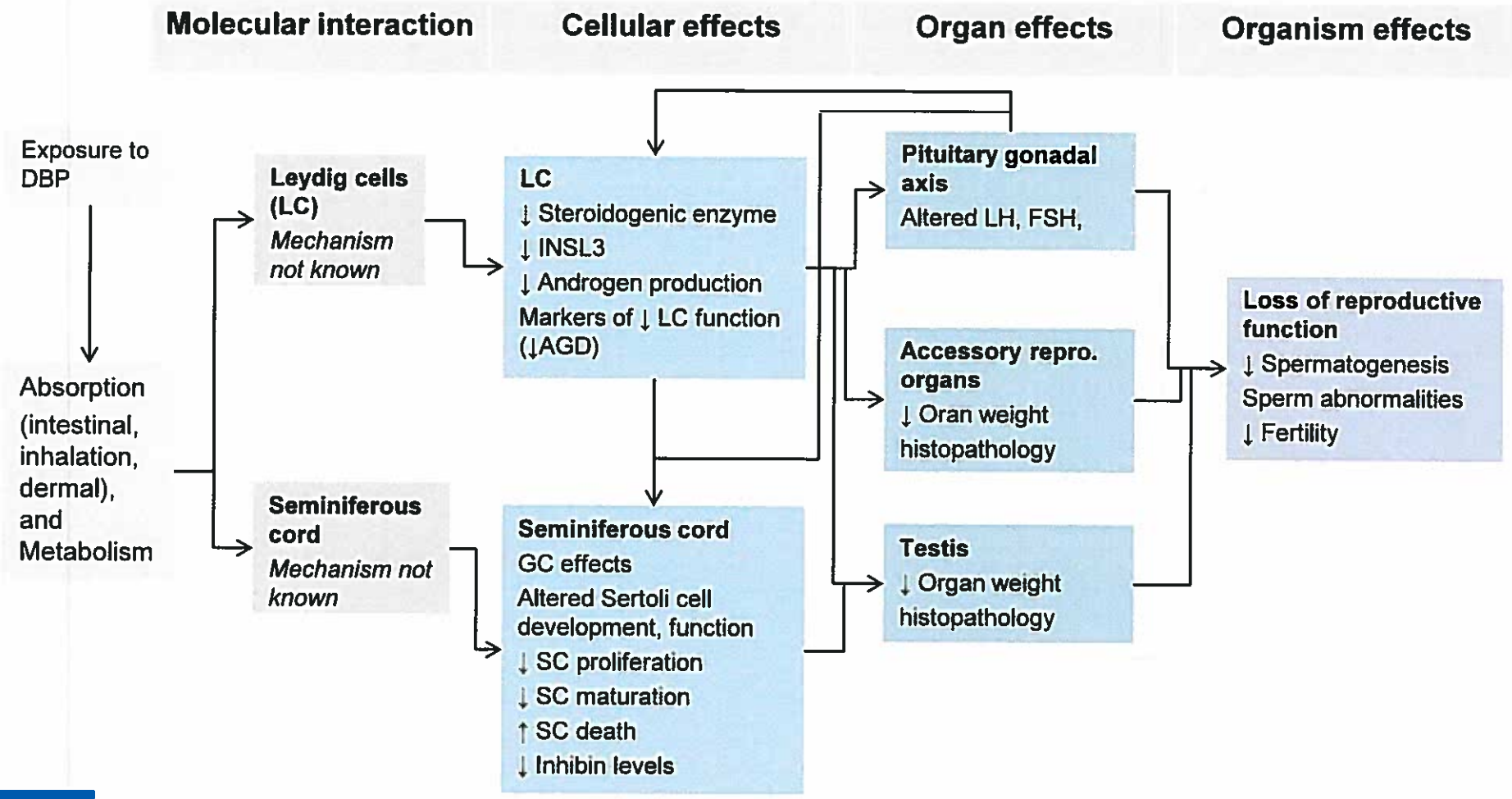
Pathway for DBP-induced male reproductive effects in early post natal life stages



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Preliminary observations early post-natal life stages

- DBP-induced Leydig cell effects are conserved in different mammalian species: (rats, rabbits, mice, gerbils, and guinea pigs, non-human primates [in-vivo and xenografts]).
- DBP-induced effects in the seminiferous cord (SC & GC) are also conserved among most mammalian models (rats, mice, and non-human primate [xenograft]).

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Utility and challenges of applying an AOP framework for this evaluation

- The AOP framework is a useful tool to gather, organize, and analyze mechanistic and toxicological information from a variety of experimental models, and levels of biological organization.
- Temporal considerations (e.g. timing of exposure and outcome evaluation) facilitates analysis of types of effects and related modes of action after exposure during specific lifestages.
- Challenges: large number of available studies, diversity of experimental models and designs, reporting gaps.

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Acknowledgements:

EPA/NCEA Phthalates team:

- Andrew Hotchkiss
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- Sue Makris
- Andre Weaver
- Christine Cai
- Todd Blessinger

EPA/NCEA Tox Pathways Workgroup

- Janice Lee
- Catherine Gibbons
- Jason Fritz
- Ravi Subramaniam
- Bob Sonawane

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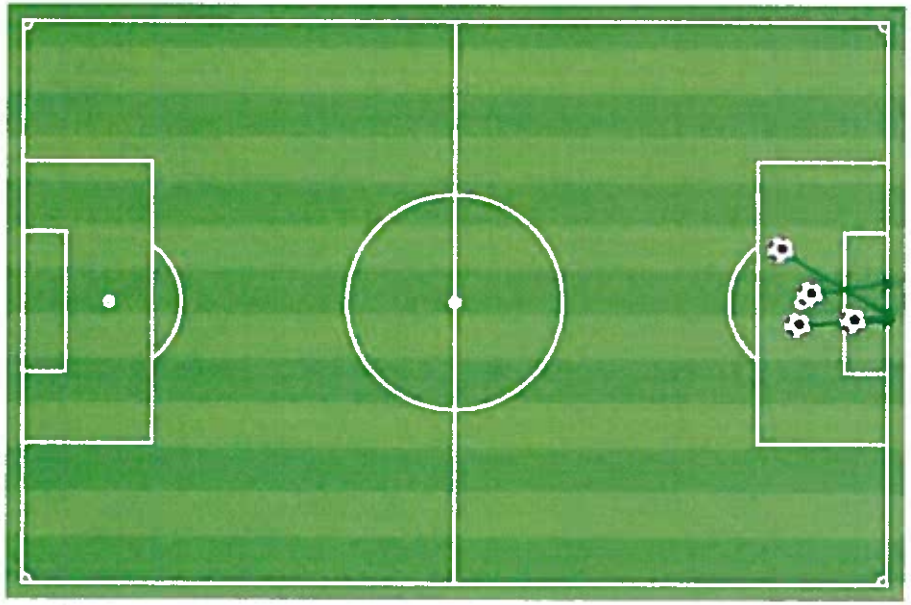
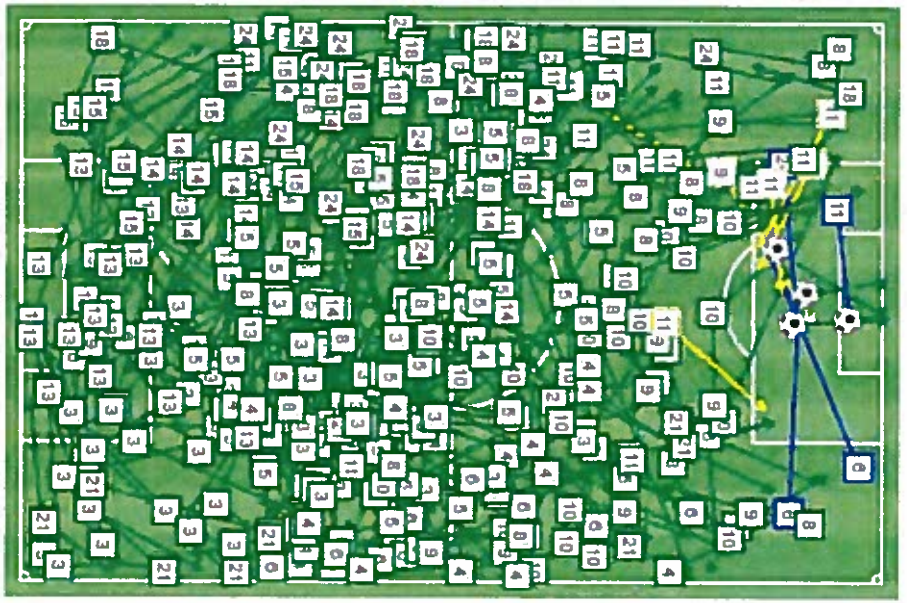
AOPs are similar to… fútbol
E.g. El Clasico: Real Madrid 0-4 Barcelona





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Summary

- Overall, the available evidence suggests that phthalate exposure during gestation and early post-natal life stages alters development of the male reproductive system.
  - Rats appear to be more sensitive to DBP-induced anti-androgenic effects during gestation.
  - DBP-induced androgen-independent responses during gestation appear to be conserved across species.
  - DBP-induced post-natal responses (LCs, GCs, SCs) also appear conserved across species.
- The AOP framework is a useful tool to integrate information from diverse experimental models, and levels of biological organization.

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Preliminary cross-species coherence analysis for gestational effects

Event	Evidence in animals	Evidence in humans (ex-vivo & xenograft)
Leydig cells (LCs)	No evidence	No evidence
Sertoli cells (SCs), germ cells (GCs)	No evidence	No evidence
LCs	+ Rat [10] & rabbits [1] - Marmosets [1] & mice [3]	- Human xenografts [3] - Human ex-vivo [1]
SCs, GCs	+ SC and GC effects in rats [12] + GC effects in rabbits [1] mice [3] - Marmoset [1]	+ Human xenografts [4]
Urethra	+ Rats [2] - Marmosets [1]	No evidence
Accessory reproductive organs	+ Rats [5] & rabbits [1] - Marmoset [1]	- Host seminiferous vesicle weight [2], prostate and LABC weight [1]
Testis	+ Rats [5] & rabbits [1] - Marmoset [1]	No evidence
Organism effects: reproductive functions	+ Rats [3] & rabbits [1] - Marmoset [1]	No evidence

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Preliminary cross-species coherence analysis for effects in pubertal and sexually mature animals

Event	Evidence in animals	Evidence in humans (ex-vivo & xenograft)
Leydig cells (LCs)	No evidence	No evidence
Sertoli cells (SCs), Germ cells (GCs)	No evidence	No evidence
LCs	+ rats [7], mice [1], rabbits [1], non-human primates [1], + LC culture models (mouse [2] & dog [1] cells), + non-human primate xenografts [1]	No evidence
SCs, GCs	+ rats (in vivo [7] and cell culture[4]), mice [2], & non-human primates xenografts [1] - non-human primates (in-vivo) [1]	No evidence
Pituitary gonadal axis	Inconsistent effects in rats [3] - Rabbits [1] or mice [1]	No evidence
Accessory reproductive organs	+ rats [3], rabbits [1], gerbils [1], & non-human primates xenograft [1] - Mice [1]	No evidence
Testis	+ rats [8], rabbits [1], mice [2], & guinea pigs [1]. - Syrian hamsters [1] mice [1].	No evidence
Reproductive functions	+ rats [4], rabbits [1], mice [1], & guinea pigs [1] - mouse [1]	No evidence.