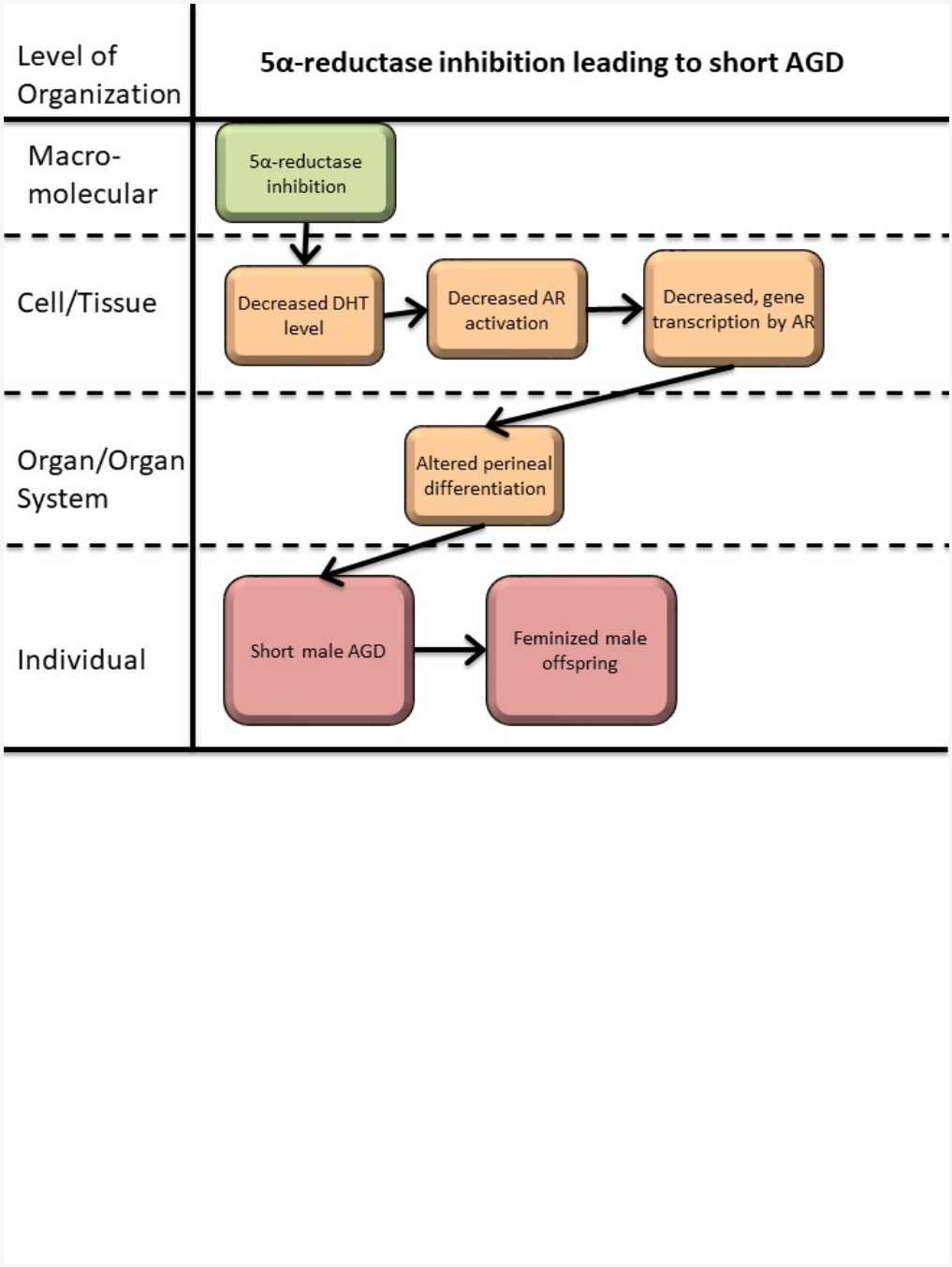
AOP ID and Title:

AOP 305: 5α-reductase inhibition leading to short anogenital distance (AGD) in male (mammalian) offspring
Short Title: 5α-reductase inhibition leading to short AGD

Graphical Representation



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Status

Author status	OECD status	OECD project	SAAOP status
Under development: Not open for comment. Do not cite	Under Development	1.90	Included in OECD Work Plan

Abstract

Abstract

This AOP links 5α-reductase inhibition during fetal life with short anogenital distance (AGD) in male offspring. A short AGD around birth is a marker for feminization of male fetuses and is associated with male reproductive disorders, including reduced fertility in adulthood. Although a short AGD is not necessarily 'adverse' from a human health perspective, it is considered an 'adverse outcome' in OECD test guidelines; AGD measurements are mandatory in specific tests for developmental and reproductive toxicity in chemical risk assessment (TG 443, TG 421/422, TG 414).

5α-reductase is an enzyme responsible for the conversion of testosterone to DHT in target tissues. DHT is more potent agonist of the Androgen receptor (AR) than testosterone, so that DHT is necessary for proper masculinization of e.g. male external genitalia. Under normal physiological conditions, testosterone produced mainly by the testicles, is converted in peripheral tissues by 5α-reductase into DHT, which in turn binds AR and activates downstream target genes. AR signaling is necessary for masculinization of the developing fetus, including differentiation of the levator ani/bulbocavernosus (LABC) muscle complex in males. The LABC complex does not develop in the absence, or low levels of, androgen signaling, as in female fetuses.

The key events in this pathway is inhibition of 5α-reductase that converts testosterone into the more potent DHT in androgen sensitive target tissues. This includes developing perineal region, which, when DHT levels are low or absent, leads to inactivation of the AR and failure to properly masculinize the perineum/LABC complex.

Summary of the AOP

Events

Molecular Initiating Events (MIE), Key Events (KE), Adverse Outcomes (AO)

Sequence	Type	Event ID	Title	Short name
1	MIE	1617	5α-reductase, inhibition	5α-reductase, inhibition
2	KE	1613	Decrease, dihydrotestosterone (DHT) level	Decrease, DHT level
3	KE	1614	Decrease, androgen receptors (AR) activation	Decrease, AR activation
	KE	286	Altered, Transcription of genes by AR	Altered, Transcription of genes by AR
5	AO	1688	decrease, male anogenital distance	short male AGD

Key Event Relationships

Upstream Event	Relationship Type	Downstream Event	Evidence	Quantitative Understanding
5α-reductase, inhibition	adjacent	Decrease, dihydrotestosterone (DHT) level	High	High
Decrease, dihydrotestosterone (DHT) level	adjacent	Decrease, androgen receptors (AR) activation		

Stressors

Name	Evidence
Finasteride	High

Finasteride

Finasteride is a type II 5alpha-reductase inhibitor that blocks conversion of testosterone to dihydrotestosterone (Clark et al 1990; Imperato-McGinley et al 1992). Intrauterine exposure in rats can result in shorter male AGD in male offspring (Bowman et al 2003; Christiansen et al 2009; Schwartz et al 2019)

References:

Bowman et al (2003), Toxicol Sci 74:393-406; doi: 10.1093/toxsci/kfg128

Christiansen et al (2009), Environ Health Perspect 117:1839-1846; doi: 10.1289/ehp.0900689

Clark et al (1990), Teratology 42:91-100; doi: 10.1002/tera.1420420111

Imperato-McGinley (1992), J Clin Endocrinol Metab 75:1022-1026; doi: 10.1210/jcem.75.4.1400866

Schwartz et al (2019), Toxicol Sci 169:303-311; doi: 10.1093/toxsci/kfz046

Overall Assessment of the AOP

Domain of Applicability

Life Stage Applicability

Life Stage	Evidence
Pregnancy	High

Taxonomic Applicability

Term	Scientific Term	Evidence	Links
human	Homo sapiens	Moderate	NCBI
rat	Rattus norvegicus	High	NCBI
mouse	Mus musculus	Moderate	NCBI

Sex Applicability

Sex	Evidence
Male	High

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Appendix 1

List of MIEs in this AOP

Event: 1617: 5α-reductase, inhibition

Short Name: 5α-reductase, inhibition

AOPs Including This Key Event

AOP ID and Name	Event Type
Aop:289 - Inhibition of 5α-reductase leading to impaired fecundity in female fish	MolecularInitiatingEvent
Aop:305 - 5α-reductase inhibition leading to short anogenital distance (AGD) in male (mammalian) offspring	MolecularInitiatingEvent

Biological Context

Level of Biological Organization
Molecular

List of Key Events in the AOP

Event: 1613: Decrease, dihydrotestosterone (DHT) level

Short Name: Decrease, DHT level

AOPs Including This Key Event

AOP ID and Name	Event Type
Aop:288 - Inhibition of 17α-hydrolase/C 10,20-lyase (Cyp17A1) activity leads to birth reproductive defects (cryptorchidism) in male (mammals)	KeyEvent
Aop:289 - Inhibition of 5α-reductase leading to impaired fecundity in female fish	KeyEvent
Aop:305 - 5α-reductase inhibition leading to short anogenital distance (AGD) in male (mammalian) offspring	KeyEvent
Aop:307 - Decreased testosterone synthesis leading to short anogenital distance (AGD) in male (mammalian) offspring	KeyEvent

Biological Context

Level of Biological Organization

Cellular

Key Event Description

Reduction in DHT synthesis leads to a reduction in DHT circulating levels. [1][2]

How it is Measured or Detected

DHT levels in a sample can be measured by (High Performance) Liquid Chromatography. After sample fractionation, DHT can be identify by comparison with internal standards spectrum. Quantification of DHT levels can be performed using hormones measurements kits (ELISA), instrumental techniques (LC-MS) or liquid scintillation spectrometry (after radiolabeling).[3]

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[2] Miller W.L. and Auchus R.J. (2011) The Molecular Biology, Biochemistry, and Physiology of Human Steroidogenesis and Its Disorders. Endocrine Reviews, 32(1): 81-151.https://doi.org/10.1210/er.2010-0013

[3] Shiraishi S., Lee P.W., Leung A., Goh V.H., Swerdloff R.S. and Wang C. (2008) Simultaneous measurement of serum testosterone and dihydrotestosterone by liquid chromatography-tandem mass spectrometry. Clinical chemistry, 54(11): 1855-63.https://doi.org/10.1373/clinchem.2008.103846

Event: 1614: Decrease, androgen receptors (AR) activation

Short Name: Decrease, AR activation

AOPs Including This Key Event

AOP ID and Name	Event Type
Aop:288 - Inhibition of 17α-hydrolase/C 10,20-lyase (Cyp17A1) activity leads to birth reproductive defects (cryptorchidism) in male (mammals)	KeyEvent
Aop:305 - 5α-reductase inhibition leading to short anogenital distance (AGD) in male (mammalian) offspring	KeyEvent
Aop:306 - Androgen receptor (AR) antagonism leading to short anogenital distance (AGD) in male (mammalian) offspring	KeyEvent
Aop:307 - Decreased testosterone synthesis leading to short anogenital distance (AGD) in male (mammalian) offspring	KeyEvent
Aop:344 - Androgen receptor (AR) antagonism leading to nipple retention (NR) in male (mammalian) offspring	KeyEvent

AOP ID and Name	Event Type
Aop:372 - Androgen receptor antagonism leading to testicular cancer	KeyEvent

Biological Context

Level of Biological Organization

Cellular

Key Event Description

Androgen receptor activation is regulated by the binding of androgens. AR activity can be decreased by either a lack of steroidal ligands (testosterone, DHT) or the presence of antagonist compounds. [1,2]

How it is Measured or Detected

Significance of AR signaling in fetal development can be studied through a conditional deletion of the androgen receptor using a Cre/loxP approach. The recommended animal model for reproductive study is the mouse.[3]

Also, epidemiological case-studies following mouse or humans expressing a complete androgen insensitivity allow to directly assess the effects of a lack of AR activation on the development.[4]

Enzyme immunoassay (ELISA) kits for in vitro quantitative measurement of AR activity are available. Androgen receptors activity can be measured using bioassay such as the (Anti-)Androgen Receptor CALUX reporter gene assay.[5]

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Event: 286: Altered, Transcription of genes by AR

Short Name: Altered, Transcription of genes by AR

Key Event Component

Process	Object	Action
regulation of gene expression	androgen receptor	decreased

AOPs Including This Key Event

AOP ID and Name	Event Type
Aop:19 - Androgen receptor antagonism leading to adverse effects in the male foetus (mammals)	KeyEvent
Aop:307 - Decreased testosterone synthesis leading to short anogenital distance (AGD) in male (mammalian) offspring	KeyEvent
Aop:344 - Androgen receptor (AR) antagonism leading to nipple retention (NR) in male (mammalian) offspring	KeyEvent

AOP ID and Name	Event Type
Aop:345 - Androgen receptor (AR) antagonism leading to decreased fertility in females	KeyEvent
Aop:305 - 5α-reductase inhibition leading to short anogenital distance (AGD) in male (mammalian) offspring	KeyEvent

Stressors

Name
Bicalutamide
Cyproterone acetate
Epoxiconazole
Flutamide
Flusilazole
Prochloraz
Propiconazole
Stressor:286 Tebuconazole
Triticonazole
Vinclozalin

Biological Context

Level of Biological Organization
Cellular

Cell term

Cell term
eukaryotic cell

Evidence for Perturbation by Stressor

Bicalutamide

Using analysis of androgen-regulated gene expression in the LNCaP prostate cancer cell line (Ngan et al. 2009).

Cyproterone acetate

Using analysis of androgen-regulated gene expression in the LNCaP prostate cancer cell line (Ngan et al. 2009) and using the AR-CALUX reporter assay in antagonism mode, cyproterone acetate showed an IC50 of 7.1 nM (Sonneveld et al. 2005).

Epoxiconazole

Using transiently AR-transfected CHO cells, epoxiconazole showed a LOEC of 1.6 mM and an IC50 of 10 mM (Kjærstad et al. 2010).

Flutamide

Analysis of androgen-regulated gene expression in the LNCaP prostate cancer cell line (Ngan et al. 2009) and using the AR-CALUX reporter assay in antagonism mode, flutamide showed an IC50 of 1.3 uM (Sonneveld et al. 2005).

Flusilazole

Using hAR-EcoScreen Assay, triticonazole showed a LOEC for antagonisms of 0.8 mM and an IC50 of 2.8 (±0.1) mM (Draskau et al. 2019)

Prochloraz

Using gene expression analysis of the androgen-regulated genes ornithine decarboxylase, prostatic binding protein C3 as well as insulin-like growth factor I. Gene expression levels were reduced in ventral prostates of male Wistar pups at postnatal day 16 following *in utero* and lactational exposure from maternal perinatal dosing with prochloraz (50 and 150 mg/kg/day) from gestational day 7 to postnatal day 16 (Laier et al. 2006). Also, using transiently AR-transfected CHO cells, prochloraz showed a LOEC of 6.3 mM and an IC50 of 13 mM (Kjærstad et al. 2010).

Propiconazole

Using transiently AR-transfected CHO cells, propiconazole showed a LOEC of 12.5 mM and an IC50 of 18 mM (Kjærstad et al. 2010).

Stressor:286 Tebuconazole

Using transiently AR-transfected CHO cells, tebuconazole showed a LOEC of 3.1 mM and an IC50 of 8.1 mM (Kjærstad et al. 2010).

Triticonazole

Using hAR-EcoScreen Assay, triticonazole showed a LOEC for antagonisms of 0.2 mM and an IC50 of 0.3 (±0.01) mM (Draskau et al. 2019).

Vinclozalin

Using the AR-CALUX reporter assay in antagonism mode, vinclozolin showed an IC50of 1.0 uM (Sonneveld et al. 2005).

Domain of Applicability

Taxonomic Applicability

Term	Scientific Term	Evidence	Links
human	Homo sapiens	High	NCBI
rat	Rattus norvegicus	High	NCBI
mouse	Mus musculus	High	NCBI

Life Stage Applicability

Life Stage	Evidence
Foetal	High
Adult, reproductively mature	High

Sex Applicability

Sex	Evidence
Mixed	High

Both the DNA-binding and ligand-binding domains of the AR are highly evolutionary conserved, whereas the transactivation domain show more divergence, which may affect AR-mediated gene regulation across species (Davey and Grossmann 2016). Despite certain inter-species differences, AR function mediated through gene expression is highly conserved, with mutation studies from both humans and rodents showing strong correlation for AR-dependent development and function (Walters et al. 2010).

This KE is applicable for both sexes, across developmental stages into adulthood, in numerous cells and tissues and across taxa.

Key Event Description

The Androgen Receptor and its function

Androgens act by binding to the Androgen receptor (AR) in androgen-responsive tissues (Davey and Grossmann 2016). Human AR mutations and mouse knockout models have established the fundamental role of AR in masculinization and spermatogenesis (Maclean et al.; Walters et al. 2010; Rana et al. 2014). The AR is also expressed in many other tissues such as bone, muscles, ovaries and within the immune system (Rana et al. 2014).

Altered transcription of genes by the AR as a Key Event

The AR belongs to the steroid hormone nuclear receptor family. It is a ligand-activated transcription factor with three domains; the N-terminal domain, the DNA-binding domain, and the ligand-binding domain with the latter being the most evolutionary conserved (Davey and Grossmann 2016). Upon activation by ligand-binding, the AR translocate from the cytoplasm to the cell nucleus, dimerizes, binds to androgen response elements in the DNA to modulate gene transcription (Davey and Grossmann 2016). The transcriptional targets varies between different cells and tissues, as well as with developmental stages and is, for instance, dependent on available co-regulators (Bevan and Parker 1999; Heemers and Tindall 2007).

Several known and proposed target genes of AR canonical signaling have been identified by analysis of gene expression following treatments with AR agonists (Bolton et al. 2007; Ngan et al. 2009) and can for instance be found in the Androgen-Responsive Gene Database (Jiang et al. 2009).

How it is Measured or Detected

In vitro

Decreased transcription of genes by the AR can be measured by measuring the transcription level of known downstream target genes by RT-qPCR or other transcription analyses approaches, eg transcriptomics.

Indirect approaches include the use of transient or stable transactivation assays including the validated OECD test guideline assay, Test No. 458: *Stably Transfected Human Androgen Receptor Transcriptional Activation Assay for Detection of Androgenic Agonist and Antagonist Activity of Chemicals* (OECD 2016). The stably transfected AR-EcoScreenTM cell line is freely available for the Japanese Collection of Research Bioresources (JCRB) Cell Bank under reference number JCRB1328. These cell-based transcriptional activation assays are typically used to detect AR agonists and antagonists. However, these types of assays are well suited to measure this KE as what they measure is exactly AR transcriptional activity. Other assays along this line include the AR-CALUX reporter gene assay that is derived from human U2-OS cells stably transfected with the human AR and an AR responsive reporter gene (van der Burg et al. 2010).

In vivo

Known downstream target gene transcription level can be measured in tissues by RT-qPCR or other gene expression analyses approaches.

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List of Adverse Outcomes in this AOP

Event: 1688: decrease, male anogenital distance

Short Name: short male AGD

Key Event Component

Process	Object	Action
androgen receptor signaling pathway	Musculature of male perineum	disrupted

AOPs Including This Key Event

AOP ID and Name	Event Type
Aop:305 - 5α-reductase inhibition leading to short anogenital distance (AGD) in male (mammalian) offspring	AdverseOutcome
Aop:306 - Androgen receptor (AR) antagonism leading to short anogenital distance (AGD) in male (mammalian) offspring	AdverseOutcome
Aop:307 - Decreased testosterone synthesis leading to short anogenital distance (AGD) in male (mammalian) offspring	AdverseOutcome

Stressors

Name
Butylparaben
p,p'-DDE
Bis(2-ethylhexyl) phthalate
Dexamethasone
Fenitrothion
Finasteride
Flutamide
Ketoconazole
Linuron
Prochloraz
Procymidone
Triticonazole
Vinclozolin
di-n-hexyl phthalate

Name
Dicyclohexyl phthalate
butyl benzyl phthalate
monobenzyl phthalate
di-n-heptyl phthalate

Biological Context

Level of Biological Organization

Tissue

Organ term

Organ term

perineum

Evidence for Perturbation by Stressor

Butylparaben

Butylparaben has been shown to cause decreased male AGD in rats following intrauterine exposure to 500 and 1000 mg/kg bw/day (Boberg et al, 2016; Zhang et al, 2014). A separate study using 600 mg/kg bw/day did not see an effect on male AGD (Boberg et al, 2008).

p,p'-DDE

p,p,DDE has been shown to cause decreased male AGD in rats following intrauterine exposure to 100-200 mg/kg bw/day (Loeffler & Peterson, 1999; Wolf et al, 1999).

Bis(2-ethylhexyl) phthalate

DEHP has been shown to cause decreased male AGD in rats following intrauterine exposure to 300-1500 mg/kg bw/day (Christiansen et al, 2010; Gray et al, 2000; Howdeshell et al, 2007; Jarfelt et al, 2005; Kita et al, 2016; Li et al, 2013; Lin et al, 2009; Moore et al, 2001; Nardelli et al, 2017; Saillenfait et al, 2009; Wolf et al, 1999).

Dexamethasone

Dexamethasone has been shown to cause decreased male AGD in rats following intrauterine exposure to 0.1 mg/kg bw/day (Van den Driesche et al, 2012).

Fenitrothion

Fenitrothion has been shown to cause decreased male AGD in rats following intrauterine exposure to 25 mg/kg bw/day (Turner et al, 2002).

Finasteride

Finasteride has been shown to cause decreased male AGD in rats following intrauterine exposure to 100 mg/kg bw/day (Bowman et al, 2003).

Flutamide

Flutamide has been shown to cause decreased male AGD in rats following intrauterine exposure to doses between 16-100 mg/kg bw/day (Foster & Harris, 2005; Hass et al, 2007; Kita et al, 2016; McIntyre et al, 2001; Mylchreest et al, 1999; Scott et al, 2007; Welsh et al, 2007).

Ketoconazole

Ketoconazole has been shown to cause decreased male AGD in rats following intrauterine exposure to 50 mg/kg bw/day in one

study (Taxvig et al, 2008), but no effect in another study using same dose (Wolf et al, 1999).

Linuron

Linuron has been shown to cause decreased male AGD in rats following intrauterine exposure to 50-100 mg/kg bw/day (Hotchkiss et al, 2004; McIntyre et al, 2002; Wolf et al, 1999).

Prochloraz

Prochloraz has been shown to cause decreased male AGD in rats following intrauterine exposure to 150-250 mg/kg bw/day (Laier et al, 2006; Noriega et al, 2005).

Procymidone

Procymidone has been shown to cause decreased male AGD in rats following intrauterine exposure to doses between 50-150 mg/kg bw/day (Hass et al, 2012; Hass et al, 2007; Wolf et al, 1999).

Triticonazole

Triticonazole has been shown to cause decreased male AGD in rats following intrauterine exposure to 150 and 450 mg/kg bw/day (Draskau et al, 2019).

Vinclozolin

Vinclozolin has been shown to cause decreased male AGD in rats following intrauterine exposure to doses between 50-200 mg/kg bw/day (Christiansen et al, 2009; Gray et al, 1994; Hass et al, 2007; Matsuura et al, 2005; Ostby et al, 1999; Schneider et al, 2011; Wolf et al, 2004).

di-n-hexyl phthalate

DnHP has been shown to cause decreased male AGD in rats following intrauterine exposure to 500-750 mg/kg bw/day (Saillenfait et al, 2009a; Saillenfait et al, 2009b).

Dicyclohexyl phthalate

DCHP has been shown to cause decreased male AGD in rats following intrauterine exposure to 350-750 mg/kg bw/day (Aydoğan Ahbab & Barlas, 2015; Hoshino et al, 2005; Saillenfait et al, 2009a).

butyl benzyl phthalate

BBP has been shown to cause decreased male AGD in rats following intrauterine exposure to 500-1000 mg/kg bw/day (Ema & Miyawaki, 2002; Gray et al, 2000; Hotchkiss et al, 2004; Nagao et al, 2000; Tyl et al, 2004).

monobenzyl phthalate

MBeP has been shown to cause decreased male AGD in rats following intrauterine exposure to 375 mg/kg bw/day (Ema et al, 2003).

di-n-heptyl phthalate

DHPP has been shown to cause decreased male AGD in rats following intrauterine exposure to 1000 mg/kg bw/day (Saillenfait et al, 2011).

Domain of Applicability

Taxonomic Applicability

Term	Scientific Term	Evidence	Links
human	Homo sapiens	Moderate	NCBI
rat	Rattus norvegicus	High	NCBI
mouse	Mus musculus	High	NCBI

Life Stage Applicability

Life Stage	Evidence
Foetal	High

Sex Applicability

Sex	Evidence
Male	High

A short AGD in male offspring is a marker of insufficient androgen action during critical fetal developmental stages (Schwartz et al, 2019; Welsh et al, 2008). A short AGD is thus a sign of undervirilization, which is also associated with a series of male reproductive disorders, including genital malformations and infertility in humans (Juul et al, 2014; Skakkebaek et al, 2001).

There are numerous human epidemiological studies showing associations with intrauterine exposure to anti-androgenic chemicals and short AGD in newborn boys alongside other reproductive disorders (Schwartz et al, 2019). This underscores the human relevance of this AO. However, in reproductive toxicity studies and chemical risk assessment, rodents (rats and mice) are what is tested on. The list of chemicals inducing short male AGD in male rat offspring is extensive, as evidenced by the 'stressor' list and reviewed by (Schwartz et al, 2019).

Key Event Description

The anogenital distance (AGD) refers to the distance between anus and the external genitalia. In rodents and humans, the male AGD is approximately twice the length as the female AGD (Salazar-Martinez et al, 2004; Schwartz et al, 2019). This sexual dimorphisms is a consequence of sex hormone-dependent development of secondary sexual characteristics (Schwartz et al, 2019). In males, it is believed that androgens (primarily DHT) activate AR-positive cells in non-myotic cells in the fetal perineum region to initiate differentiation of the perineal *levator ani* and *bulbocavernosus* (LABC) muscle complex (Ipulan et al, 2014). This AR-dependent process occurs within a critical window of development, around gestational days 15-18 in rats (MacLeod et al, 2010). In females, the absence of DHT prevents this masculinization effect from occurring.

The involvement of androgens in masculinization of the male fetus, including the perineum, has been known for a very long time (Jost, 1953), and AGD has historically been used to, for instance, sex newborn kittens. It is now well established that the AGD in newborns is a proxy readout for the intrauterine sex hormone milieu the fetus was developing. Too low androgen levels in XY fetuses makes the male AGD shorter, whereas excess (ectopic) androgen levels in XX fetuses makes the female AGD longer, in humans and rodents (Schwartz et al, 2019).

How it is Measured or Detected

The AGD is a morphometric measurement carried out by trained technicians (rodents) or medical staff (humans).

In rodent studies AGD is assessed as the distance between the genital papilla and the anus, and measured using a stereomicroscope with a micrometer eyepiece. The AGD index (AGDi) is often calculated by dividing AGD by the cube root of the body weight. It is important in statistical analysis to use litter as the statistical unit. This is done when more than one pup from each litter is examined. Statistical analyses is adjusted using litter as an independent, random and nested factor. AGD are analysed using body weight as covariate as recommended in Guidance Document 151 (OECD, 2013).

Regulatory Significance of the AO

In regulatory toxicology, the AGD is mandatory inclusions in OECD test guidelines used to test for developmental and reproductive toxicity of chemicals. Guidelines include 'TG 443 extended one-generation study', 'TG 421/422 reproductive toxicity screening studies' and 'TG 414 developmental toxicity study'.

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Appendix 2

List of Key Event Relationships in the AOP

List of Adjacent Key Event Relationships

Relationship: 1880: 5α-reductase, inhibition leads to Decrease, DHT level

AOPs Referencing Relationship

AOP Name	Adjacency	Weight of Evidence	Quantitative Understanding
Inhibition of 5α-reductase leading to impaired fecundity in female fish	adjacent	High	High
5α-reductase inhibition leading to short anogenital distance (AGD) in male (mammalian) offspring	adjacent	High	High

Relationship: 1935: Decrease, DHT level leads to Decrease, AR activation

AOPs Referencing Relationship

AOP Name	Adjacency	Weight of Evidence	Quantitative Understanding
Inhibition of 17α-hydrolase/C 10,20-lyase (Cyp17A1) activity leads to birth reproductive defects (cryptorchidism) in male (mammals)	adjacent	High	High
Decreased testosterone synthesis leading to short anogenital distance (AGD) in male (mammalian) offspring	adjacent	High	Moderate
5α-reductase inhibition leading to short anogenital distance (AGD) in male (mammalian) offspring	adjacent		

Evidence Supporting Applicability of this Relationship

Taxonomic Applicability

Term	Scientific Term	Evidence	Links
mammals	mammals	High	NCBI
human	Homo sapiens	High	NCBI
mouse	Mus musculus	High	NCBI
rat	Rattus norvegicus	High	NCBI

Life Stage Applicability

Life Stage	Evidence
Foetal	High
During development and at adulthood	High

Sex Applicability

Sex	Evidence
Male	High

Key Event Relationship Description

Dihydrotestosterone (DHT) is, together with testosterone, a primary ligand for the Androgen receptor (AR). DHT is an endogenous sex hormone that is synthesis from e.g. testosterone by the enzyme 5α-reductase in selected tissues, not least in the reproductive tracts of both sexes, but also other tissues and organs (Davey & Grossmann, 2016; Marks, 2004). In the absence of ligand (DHT/testosterone) the AR is localized in the cytoplasm. AR is only activated and translocated into the nucleus to carry out its 'genomic function' upon ligand binding (Davey & Grossmann, 2016). Hence, AR transcriptional function is directly dependent on the presence of ligands, with DHT being a more potent AR activator (2-fold higher binding affinity) than testosterone (Grino et al, 1990). Reduced levels of DHT will lead to reduced AR activation.