Do Flame Retardants Impact Men's Hormones?

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Testosterone Target Organs

Skin
Male pattern body and facial hair, balding, sebum production

Brain
• libido
• aggression

Liver
• synthesis of serum proteins

Muscle
• increase in strength and volume

Male accessory organs
• penile growth,
  • spermatogenesis,
  • prostate growth and function

Kidney
• stimulation of erythropoietin production

Bone marrow
• stimulation of stem cells

Bone
• accelerated linear growth
• closure of epiphyses

Adapted from Medscape
Figure from: Amazon.com: New Fashion Figure Templates: Over 250 Templates (9780713490336): Patrick John Ireland: Books
How do Endocrine disruptors work?

- They can mimic the action of naturally occurring hormones.
  - sets off similar chemical reactions in the body

- They can block hormone receptors.
  - prevents the action of normal hormones

- They can affect the synthesis, transport, metabolism and excretions of hormones.
  - alters the concentration of natural hormones

Decreasing serum Testosterone levels increases the incidence of osteoporosis

HBCD (hexabromocyclododecane) exposure in male rats:
• decreased bone length
• decreased total mineral content, total area, cortical area, and cortical thickness

van der Ven et al., 2009. Toxicol Lett 185, 51-62
Endocrine Disruptors can Modify the Testis Germ Cell Niche

Leydig cells

peritubular myoid cells

Sertoli cells

Spermatogenesis

Spermatogonia

Spermatocytes

Round spermatids

Mature sperm

testosterone

Kopras, E and Kasper S, 2013. Endocrine Related Cancer, in press

B - BPA
D - DEHP
E - E2
M - MEHP
P - paraben
S - SCOTP
T - TOCP
V - Vinclozolin
FRs alter the quantity and quality of sperm.

TCP:
- male Long Evans rats
- ↓ sperm concentration
- ↓ sperm motility and progressive movement
- abnormal sperm morphology

Tris-BP:
- mutagenic assay using B6C3F mice
- ↑ abnormalities in the sperm head (implies genetic damage)

DMMP:
- male Fischer 344 rats
- ↑ sperm resorption with increasing doses of DMMP
- lack of spermatogenesis (at high doses)

FR components exhibit multiple endocrine disrupting activities

Firemaster 550 and Saytex BC-4 components:
• TBB (2-ethylhexyl-2,3,4,5-tetrabromobenzoate)
• TBPH (Bis(2-ethylhexyl)-2,3,4,5-tetrabromophtalate),
• TBCO (1,2,5,6-tetrabromocyclooctane)

TBB - antiestrogenic [effect of 62% at 0.5mgL(-1) in the YES assay]

TBPH and TBCO - antiandrogenic [effects of 74% and 59% at 300mgL(-1) and 1500mgL(-1), respectively, in the YAS assay].

PBDEs (Polybrominated diphenyl ethers) – estrogenic
• associated with menarche at an earlier age (before 12 years of age)

BDE100 (2,2',4,4',6-Pentabromodiphenylether)
• Antiandrogenic
• Antiestrogenic
• Gene promoter dependent

Firefighters have a **probable** cancer risk for:

<table>
<thead>
<tr>
<th>Cancer</th>
<th>summary risk estimate (SRE)</th>
<th>95% confidence interval (CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>multiple myeloma</td>
<td>1.53</td>
<td>1.21 - 1.94</td>
</tr>
<tr>
<td>non-Hodgkin lymphoma</td>
<td>1.51</td>
<td>1.31 - 1.73</td>
</tr>
<tr>
<td>prostate</td>
<td>1.28</td>
<td>1.15 - 1.43</td>
</tr>
<tr>
<td>testicular</td>
<td>2.02</td>
<td>1.30 - 3.13</td>
</tr>
</tbody>
</table>

- Firefighters present with prostate cancer (PCa) at least 15 to 20 years earlier than the general male population (Grace LeMasters, personal communication).

- Firefighters can present with PCa as early as in their late 30s and 40s (Cindy Ell, Executive Director, Fire Fighter Cancer Foundation, personal communication).

Testosterone Activity and Levels with Aging

Changes in the T/E Ratio can promote prostate cancer

DHT = dihydrotestosterone
E₂ = estradiol
T = testosterone

http://www.drjohntafel.com/?page_id=294
Early exposure to estrogen and BPA promotes the growth of prostate cancer in later life.

Which prostate cells are targeted by flame retardant exposure?

<table>
<thead>
<tr>
<th>Stage of Disease</th>
<th>Target Cells/Tissues</th>
</tr>
</thead>
<tbody>
<tr>
<td>“normal” prostate</td>
<td>Benign Prostatic Hyperplasia (BPH)</td>
</tr>
<tr>
<td>lo/med grade prostate cancer</td>
<td>Prostate cancer ($\leq$ Gleason score 6)</td>
</tr>
<tr>
<td>hi grade prostate cancer</td>
<td>Prostate cancer ($\geq$ Gleason score 8)</td>
</tr>
<tr>
<td>Metastatic cancer</td>
<td>Cancer Stem Cells (CSCs)</td>
</tr>
<tr>
<td></td>
<td>Circulating Tumor Cells (CTCs)</td>
</tr>
</tbody>
</table>
FRs stimulate prostate cancer stem cell growth and expansion

- 0.1% of tumor cells
- they can remake themselves over and over again
- they do not respond to androgen deprivation therapy

control

+ FR

CSC expansion
FRs inhibit androgen-regulated gene expression in the bulk of the tumor cells

- >99% of tumor cells
- limited cell proliferation
- responsive to androgen deprivation therapy

Inhibition of androgen activity
FR activity differentially regulates prostate cancer stem cell and tumor cell growth and/or function.

>99% of tumor cells

0.1% of tumor cells

Emergence of treatment resistant prostate cancer
Effects of Flame Retardant Exposure

- FRs bind to and activate many different steroid hormone receptors.

- FRs can function as androgens, antiandrogens, estrogens and/or antiestrogens, thereby disrupting the development and function of male accessory organs, bone, etc.

- FRs may promote prostate cancer progression by disrupting testosterone and estrogen activity and/or expression.

- FRs could stimulate prostate cancer stem cell growth promote the emergence of treatment-resistant cancer.
Challenges for defining the effects of FRs on our health:

- Developing models relevant to human disease
- Identifying the lowest permissible biological dose
- Establishing the biological effects of FRs \textit{in vivo}
- Discovering cell-based biomarkers for assessing FR exposure
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