Endocrine disrupting activity associated with unconventional oil and natural gas operations

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1. Can chemicals used in oil and gas extraction disrupt normal endocrine signals?
2. Is endocrine disrupting activity in surface and ground water associated with oil and gas extraction?
3. What Health effects may be associated with exposure to chemicals?
Steroid Hormones

- Estradiol
- Testosterone
- Progesterone
- Cortisol
- Aldosterone
Estrogen receptor is a ligand activated transcription factor.
Hormones can work at low concentrations

1 drop in olympic pool = 1 part per billion
Normal Function of 5 Hormones

- **Estrogen**
  - Sexual Differentiation
  - Weight, appetite, energy
  - Fertility, Pregnancy
  - Puberty, Secondary Sex Characteristics
  - Organ Development and Maintenance
  - Brain Development
  - Cell Proliferation
  - Muscle and Bone

- **Androgen**

- **Glucocorticoid**

- **Progesterone**

- **Thyroid**
Endocrine Disrupting Chemicals (EDC)

“A chemical, or mixture of chemicals, that interferes with any aspect of hormone action.”

The Endocrine Society Statement on endocrine disrupting chemicals. Endocrinology 2012
EDCs can disrupt hormone receptors
EDCs are found in many products

- Metals
- Industrial Chemicals
- Personal Care Products
- Endocrine Disrupting Chemicals
- Synthetic & Natural hormones
- Pesticides
- Herbicides
- Pharmaceutical chemicals
Why is endocrine disruption important to human health and disease?

- Hormones and EDCs can act at low concentrations
- Human exposure can be within the range of bioactivity
- Developmental exposure can alter adult health & disease
Disruption of hormones can result in adverse health outcomes

- Estrogen
- Androgen
- Glucocorticoids
- Progesterone
- Thyroid
- Cancer
- Metabolic Syndrome
- Immune Disorders
- Infertility
- Altered Puberty
- Reproductive Problems
- Neurological Issues
- Behavioral Disorders
- Organ Defects
1. Can chemicals used in unconventional oil and gas (UOG) operations disrupt normal endocrine signals?

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Our hypothesis: Chemicals used in hydraulic fracturing will disrupt hormone receptors

- Estrogen
- Androgen
- Glucocorticoid
- Progesterone
- Thyroid

Chris Kassotis, PhD
EDC activity measured with nuclear receptor reporter gene assay

- Tested 24 chemicals
- Five nuclear receptors
- Measured receptor activation
- Measured receptor inhibition
<table>
<thead>
<tr>
<th>Chemical Name</th>
<th>CAS #</th>
<th>Oil and Gas Operation Use</th>
</tr>
</thead>
<tbody>
<tr>
<td>1,2,4-trimethylbenzene</td>
<td>95-63-6</td>
<td>Surfactant</td>
</tr>
<tr>
<td>2-(2-methoxyethoxy) ethanol</td>
<td>111-77-3</td>
<td>Biocide, Surfactant</td>
</tr>
<tr>
<td>2-ethylhexanol</td>
<td>104-76-7</td>
<td>Defoamer, Breaker</td>
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<tr>
<td>Acrylamide</td>
<td>79-06-1</td>
<td>Scale Control, Friction Reducer</td>
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<tr>
<td>Benzene</td>
<td>71-43-2</td>
<td>Paraffin Inhibitor, Surfactant</td>
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<tr>
<td>Bronopol</td>
<td>52-51-7</td>
<td>Biocide</td>
</tr>
<tr>
<td>Cumene (Isopropylbenzene)</td>
<td>98-82-8</td>
<td>Paraffin Inhibitor</td>
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<tr>
<td>Diethanolamine</td>
<td>111-42-2</td>
<td>Friction Reducer, Corrosion Inhibitor</td>
</tr>
<tr>
<td>Dimethylformamide</td>
<td>68-12-2</td>
<td>Corrosion Inhibitor</td>
</tr>
<tr>
<td>Ethoxylated nonylphenol</td>
<td>9016-45-9</td>
<td>Surfactant, Corrosion Inhibitor</td>
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<tr>
<td>Ethoxylated octylphenol</td>
<td>9036-19-5</td>
<td>Surfactant, Corrosion Inhibitor</td>
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<tr>
<td>Ethylbenzene</td>
<td>100-41-4</td>
<td>Non-emulsifier, paraffin inhibitor</td>
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<tr>
<td>Ethylene glycol</td>
<td>107-21-1</td>
<td>Crosslinker, Friction reducer</td>
</tr>
<tr>
<td>Ethylene glycol monobutyl ether (2-BE)</td>
<td>111-76-2</td>
<td>Surfactant, Foamer</td>
</tr>
<tr>
<td>Methyl-4-isothiazolin</td>
<td>2682-20-4</td>
<td>Biocide</td>
</tr>
<tr>
<td>Naphthalene</td>
<td>91-20-3</td>
<td>Surfactant, Acid Inhibitor</td>
</tr>
<tr>
<td>Phenol</td>
<td>108-95-2</td>
<td>Resin-coating for proppants</td>
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<tr>
<td>Propylene glycol</td>
<td>57-55-6</td>
<td>Gellant, Breaker</td>
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<tr>
<td>Sodium tetraborate decahydrate</td>
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<td>Crosslinker</td>
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<td>Styrene</td>
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<td>Proppant</td>
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<tr>
<td>Toluene</td>
<td>108-88-3</td>
<td>Non-emulsifier, paraffin inhibitor</td>
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<tr>
<td>Triethylene glycol</td>
<td>112-27-6</td>
<td>Biocide, Dehydration</td>
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<tr>
<td>Xylenes</td>
<td>1330-20-7</td>
<td>Non-emulsifier, Breaker</td>
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</tbody>
</table>
## EDC Activity of 24 Fracking Chemicals

<table>
<thead>
<tr>
<th>Receptor</th>
<th>Activation</th>
<th>Inhibition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Estrogen</td>
<td>1</td>
<td>21</td>
</tr>
<tr>
<td>Androgen</td>
<td>0</td>
<td>21</td>
</tr>
<tr>
<td>Progesterone</td>
<td>1</td>
<td>12</td>
</tr>
<tr>
<td>Glucocorticoid</td>
<td>0</td>
<td>10</td>
</tr>
<tr>
<td>Thyroid</td>
<td>2</td>
<td>7</td>
</tr>
</tbody>
</table>

1. Can chemicals used in unconventional oil and gas (UOG) operations disrupt normal endocrine signals?

2. Is endocrine disrupting activity in surface and ground water associated with UOG extraction?

3. What Health effects may be associated with exposure to chemicals?
Oil and Gas Waste Water Injection Disposal Facility in West Virginia
Surface Water Antagonist Activities

Endocrine disrupting activities of surface water associated with a West Virginia oil and gas industry wastewater disposal site

Christopher D. Kassotis a,*, Luke R. Iwanowicz b, Denise M. Akob c, Isabelle M. Cozzarelli c, Adam C. Mumford c, William H. Orem d, Susan C. Nagel e,***

Chris Kassotis, PhD

Denise Akob, PhD
1. Can chemicals used in unconventional oil and gas (UOG) operations disrupt normal endocrine signals?

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Fetal and early life exposure to EDCs is associated with adult disease
Developmental exposure to a mixture of 23 UOG chemicals via drinking water

Vehicle 0.2% ethanol
Mix 1 3000 µg/kg
Mix 2 300 µg/kg
Mix 3 30 µg/kg
Mix 4 3 µg/kg
Activity of Chemical Mixture

(B) Antagonist Receptor Activities of 23-mix

% Activity of Receptor Agonist vs. Chemical Concentration (M)

- Ec50
- Glucocorticoid
- Estrogen
- Androgen
- Progesterone
- Thyroid

Kassotis, et al, 2015
Prenatal exposure to UOG mixture increased altered body and organ weights in adult male mice

Kassotis et al 2015, Endocrinology

Ground water directly below surface spills, Gross et al

Kassotis et al 2015, Endocrinology
Prenatal exposure to UOG mixture increased testis weight

Kassotis et al 2015, Endocrinology
Prenatal exposure to UOG mixture increased adult testosterone and decreased sperm counts.
Prenatal Exposure: Prolactin and FSH Levels in Females

Kassotis et al 2016 Submitted
Prenatal Exposure: LH and Increases GH in females

Kassotis et al 2016 Submitted
Does maternal exposure alter embryo development

![Diagram of treatment timeline](image_url)
Maternal exposure to mixture and embryo abnormalities
Fetal and early life exposure to EDCs is associated with adult disease

Pollutants → Nutritional → Maternal Health and Disease → Infertility

Obesity
Heart Disease
Diabetes
Hypertension
Hyperactivity
Bone Health
Endometriosis
Breast Cancer
Testicular Cancer
Exposure

- Start HFD diet
- Start Metabolic Cages
- Necropsy

Days:
- GD0
- GD1
- PND7
- PND21
- 11 months

High Fat Diet
- Day 0
- Day 3
- Day 6

Authors:
- John Thyfault
- Tori Balise
Exposure

C57Bl6 were exposed to either a vehicle or 1 of 4 different concentrations of equimolar mixture of 23 chemicals.

Treatments:
- Vehicle
- 1.5 ug/kg/day
- 15 ug/kg/day
- 150 ug/kg/day
- 1500 ug/kg/day
Sable Systems Metabolic Cages
Perinatal exposure: energy expenditure in adulthood

Light Cycle
**Perinatal exposure: activity in adulthood**

<table>
<thead>
<tr>
<th>Spontaneous Activity</th>
<th>Meters Travelled</th>
</tr>
</thead>
</table>

* * P<.05  ** ** P<.0125
Adiposity

Perirenal fat pad  Periuterine fat pad

* P<.05  ** P<.0125
Perinatal exposure: recovery after glucose challenge
Elevated Plus Maze

Paola Palanza
http://www.nature.com/scitable/knowledge/library/rapid-effects-of-steroid-hormones-on-animal-15104619
Perinatal Exposure: Exploratory Behavior
Conclusions

• Oil and gas activities use and produce EDCs
• EDC activity in surface and ground water is associated with oil and gas activities
• Laboratory studies suggest a potential for negative impacts on health from exposure to these chemicals
Funding: The Passport Foundation, University of Missouri, EPA STAR Fellowship to Kassotis, NIH NIEHS R21