Figure 1. F causes dysfunction of spermatozoa by three mechanisms, i.e., oxidative stress, zinc deficiency, disturbed signaling transduction.
Figure 2. F interferes with spermatogenesis through five mechanisms.

<table>
<thead>
<tr>
<th>No.</th>
<th>Species</th>
<th>Dose</th>
<th>Length of exposure</th>
<th>Effect</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Rabbit</td>
<td>10 mg NaF/kg bw/day</td>
<td>18 mo</td>
<td>Structural defects in various organelles in spermatozoa e.g., flagella, acrosome, and mitochondria</td>
<td>6</td>
</tr>
<tr>
<td>2</td>
<td>Rat</td>
<td>4.5 ppm or 9 ppm NaF DW&lt;sup&gt;a&lt;/sup&gt;</td>
<td>75 Days</td>
<td>Decrease in sperm motility and steroidogenic enzymes</td>
<td>4</td>
</tr>
<tr>
<td>3</td>
<td>Mouse</td>
<td>10 mg NaF/kg bw/day</td>
<td>?</td>
<td>A significant decline in sperm acrosomal acrosin and hyaluronidase</td>
<td>21</td>
</tr>
<tr>
<td>4</td>
<td>Rat</td>
<td>5 mg F/kg bw/day</td>
<td>8 Weeks</td>
<td>Altered plasma membrane, and deceased ability to undergo acrosome reaction and oocyte fertilization</td>
<td>22</td>
</tr>
<tr>
<td>5</td>
<td>Rat</td>
<td>10 mg NaF/kg bw/day</td>
<td>30 or 50 Days</td>
<td>Disturbances in energy metabolism in vas deferens and seminal vesicle</td>
<td>8</td>
</tr>
<tr>
<td>6</td>
<td>Rat</td>
<td>5 mg F/kg bw/day; F in serum: 0.263±0.024 ppm</td>
<td>8 Weeks</td>
<td>Oxidative stress and loss of mitochondrial transmembrane potential</td>
<td>25</td>
</tr>
<tr>
<td>7</td>
<td>Mouse</td>
<td>50, 100, 200, 300 mg NaF/L DW</td>
<td>8 Weeks</td>
<td>Reduced antioxidative defense and oxidative stress, in two high dose groups, distinct testis cell apoptosis</td>
<td>26</td>
</tr>
<tr>
<td>8</td>
<td>Rat</td>
<td>5 or 26 mg F/L DW</td>
<td>12 Weeks</td>
<td>Free radical toxicity in testis</td>
<td>27</td>
</tr>
<tr>
<td>9</td>
<td>Rat</td>
<td>100 or 200 ppm F DW</td>
<td>16 Weeks</td>
<td>Decreased zinc concentrations in testis</td>
<td>36</td>
</tr>
<tr>
<td>10</td>
<td>Bank Vole</td>
<td>200 mg F/mL DW</td>
<td>4 mo</td>
<td>Decreased testicular zinc concentration</td>
<td>37</td>
</tr>
<tr>
<td>11</td>
<td>Bank Vole</td>
<td>200 mg/mL F DW plus moderate photo period</td>
<td>4 mo</td>
<td>Decreased zinc concentration in testis</td>
<td>38</td>
</tr>
<tr>
<td>12</td>
<td>Mouse</td>
<td>10 or 100 ppm F DW</td>
<td>3 mo</td>
<td>Decreased sperm head tyrosine phosphorylation and actin polymerization</td>
<td>42</td>
</tr>
<tr>
<td>13</td>
<td>Mouse</td>
<td>150 mg NaF/L DW</td>
<td>7 Weeks</td>
<td>Decreased sperm hyperactivation and Catsper1 gene expression level</td>
<td>46</td>
</tr>
<tr>
<td>14</td>
<td>Rabbit</td>
<td>10 mg NaF/kg bw/day</td>
<td>18 or 29 mo</td>
<td>In 29-mo group, F crossed the blood-testis barrier; cessation of spermatogenesis.</td>
<td>49</td>
</tr>
<tr>
<td>15</td>
<td>Mouse</td>
<td>1000 ppm NaF DW</td>
<td>3 mo</td>
<td>Necrosis of seminiferous tubules, lack of maturation and differentiation of spermatocytes, and cessation of spermatogenesis.</td>
<td>50</td>
</tr>
<tr>
<td>16</td>
<td>Rabbit</td>
<td>10 mg NaF/kg</td>
<td>23 mo</td>
<td>Fragmentation of spermatozoa in</td>
<td>13</td>
</tr>
<tr>
<td></td>
<td>Species</td>
<td>Treatment</td>
<td>Duration</td>
<td>Effects</td>
<td></td>
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</tr>
<tr>
<td>17</td>
<td>Rat</td>
<td>20 mg NaF/kg bw/day</td>
<td>28 Days</td>
<td>Inhibition of spermatogenesis and significant diminution in steroidogenic enzymes (3β-HSD, 17βHSD)</td>
<td></td>
</tr>
<tr>
<td>18</td>
<td>Rat</td>
<td>50 mg/50 mL NaF into vas deferens</td>
<td>Single injection</td>
<td>Arrest of spermatogenesis and absence of spermatozoa in ST&lt;sup&gt;1&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>19</td>
<td>Rat</td>
<td>150 mg NaF/L DW</td>
<td>10 Days</td>
<td>Decreased expression of EGF &amp; EGFR in spermatogenic and Leydig cells</td>
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</tr>
<tr>
<td>20</td>
<td>Rat</td>
<td>4.5 mg NaF/kg bw/day</td>
<td>60 Days</td>
<td>Decreased diameter of ST</td>
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<tr>
<td>21</td>
<td>Rat</td>
<td>150 mg NaF/L DW</td>
<td>50, 100 or 120 Days</td>
<td>Decrease in diameter of ST and number of seminiferous epithelial cell layers</td>
<td></td>
</tr>
<tr>
<td>22</td>
<td>Mous</td>
<td>10 or 20 mg NaF/kg bw/day</td>
<td>30 Days</td>
<td>Severe disorganization and denudation of germinal epithelial cells in ST</td>
<td></td>
</tr>
<tr>
<td>23</td>
<td>Human</td>
<td>3-27 mg F/day bw/day or 2-13 mg F/day bw/day</td>
<td>Long Time</td>
<td>A significant reduction in T&lt;sup&gt;2&lt;/sup&gt; and increase in FSH</td>
<td></td>
</tr>
<tr>
<td>24</td>
<td>Human</td>
<td>Fluorosis</td>
<td>Long Time</td>
<td>Decrease in T, increase in FSH and LH</td>
<td></td>
</tr>
<tr>
<td>25</td>
<td>Rat</td>
<td>Subcutaneous injection of NaF solution</td>
<td>28 or 38 Days</td>
<td>Decrease in serum estradiol level and apoptosis of spermatogenic cells</td>
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<tr>
<td>26</td>
<td>Human</td>
<td>1.52-6.95 mg NaF/L DW; F in serum: 0.216±0.060 ppm</td>
<td>Long Time</td>
<td>Altered conversion of testosterone into potent metabolite</td>
<td></td>
</tr>
<tr>
<td>27</td>
<td>Rat</td>
<td>0.1 or 1.0 mg F daily</td>
<td>2 mo</td>
<td>Decrease in T4 and T3 level in plasma</td>
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<tr>
<td>28</td>
<td>Human</td>
<td>122±5 mumol/L or 52±5 mumol/L F DW</td>
<td>Long Time</td>
<td>Elevated TSH, decrease in T3</td>
<td></td>
</tr>
<tr>
<td>29</td>
<td>Rat</td>
<td>30 mg F/L DW</td>
<td>?</td>
<td>Decrease in T3, T4, and thyroid peroxidase</td>
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</tr>
<tr>
<td>30</td>
<td>Rat</td>
<td>150 mg F/L DW</td>
<td>120 Days</td>
<td>Decrease in T3 and T4; flattened follicular epithelial cells</td>
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<tr>
<td>31</td>
<td>Rat</td>
<td>20 mg NaF/kg bw/day</td>
<td>29 Days</td>
<td>Oxidative stress; decrease in T and steroidogenic enzymes</td>
<td></td>
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<tr>
<td>32</td>
<td>Human</td>
<td>Skeletal fluorosis</td>
<td>Long Time</td>
<td>A significant reduction in T</td>
<td></td>
</tr>
<tr>
<td>33</td>
<td>Mous</td>
<td>200 or 300 mg NaF/L DW</td>
<td>8 Weeks</td>
<td>Decrease in AR expression</td>
<td></td>
</tr>
<tr>
<td>34</td>
<td>Rat</td>
<td>10 mg NaF/kg bw/day</td>
<td>50 Days</td>
<td>Significant change in diameter of Leydig cells, reduced steroidogenic enzymes, and disturbance in steroidogenesis</td>
<td></td>
</tr>
<tr>
<td>35</td>
<td>Rabbit</td>
<td>4.5 mg/kg bw/day</td>
<td>?</td>
<td>Degenerative changes in Leydig cells</td>
<td></td>
</tr>
</tbody>
</table>
| 36 | Rat     | 30 or 100 mg F/L DW | 8 Weeks | Disturbed hormone levels of each layer of the hypothalamus-
<p>| | | | | | | |</p>
<table>
<thead>
<tr>
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<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>37</td>
<td>Human</td>
<td>F in pineal gland: 297±257 mg F/kg</td>
<td>Long Time</td>
<td>Accumulation of F in pineal gland</td>
<td>89</td>
<td></td>
</tr>
<tr>
<td>38</td>
<td>Gerbil HiF*: 37 mg F/kg bw/day in food. LF*: 7 mg F/kg bw/day in food</td>
<td>7, 9, 11.5, 16 Weeks</td>
<td>Depressed pineal melatonin output</td>
<td>3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>39</td>
<td>Human</td>
<td>1.52-6.95 mg NaF/L DW; F in serum: 0.216±0.060 ppm</td>
<td>Long Time</td>
<td>Fluorosis, significant increase in serum catecholamines, and stimulatory effect on sympathetic nervous system.</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>40</td>
<td>Chick</td>
<td>500, 1000, 1500, 2000 mg F/kg in food</td>
<td>150 Days</td>
<td>Karyopyknosis, decreased microvilli and swollen vacuoles in epithelial follicular cells</td>
<td>110</td>
<td></td>
</tr>
<tr>
<td>41</td>
<td>Mouse</td>
<td>500 ppm NaF DW to mother mice</td>
<td>Duration f</td>
<td>For the suckling pups: decreased colloid volume</td>
<td>111</td>
<td></td>
</tr>
<tr>
<td>42</td>
<td>Pig</td>
<td>100, 250 or 400 mg F/kg in food</td>
<td>50 Days</td>
<td>Decrease in activities of Na/K-ATPase and thyroid peroxidase (TPO)</td>
<td>114</td>
<td></td>
</tr>
</tbody>
</table>

*a* DW: drinking water; *b* ST: seminiferous tubules; *c* T: testosterone; *d* HiF: high F; *e* LF: low F; *f* Duration: from 15th day of pregnancy to 4th or 14th day after parturition.

**Definitions:**

Acrosome: A caplike structure at the anterior end of a spermatozoon that produces enzymes (acrosin and hyaluronidase) aiding in dissolution of the zona pellucida of an ovum in order to facilitate the fusion of two gametes.

Capacitation: changes made by sperm which enable them to penetrate eggs

EGF: Epidermal Growth Factor

Karyopyknosis: shrinkage of the nucleus of a cell with the condensation of the chromatin into structureless masses