Genistein induced a dose-dependent increase in multi-oocyte follicles in WT CD-1 mice treated for 5 days with genistein when compared to vehicle controls (Table 2). 49 Given the established tyrosine kinase inhibitory activity of genistein, the nonestrogenic tyrosine kinase inhibitor lavendustin A was incorporated into these experiments to confirm that the results were due solely to the associated estrogenic activity of genistein. No multi-oocyte follicles were observed in mice treated with two different concentrations of lavendustin A, indicating that the genistein-induced increases in multi-oocyte follicles were due to its estrogenic activity and not to tyrosine kinase inhibition. Further experiments were conducted in C57BL/6, αERKO, and βERKO mice to determine if genistein signaling in the ovary is mediated by ERα, ERβ, or a non-receptor-mediated mechanism. Results from these studies showed that genistein induced a concentration-dependent increase in multi-oocyte follicles in C57BL/6 and αERKO mice, while the incidence of multi-oocyte follicles in βERKO mice was significantly lower. 49 These results indicate that ERβ is necessary for the induction of multi-oocyte follicles in genistein-treated neonatal mice.

Taken together, these in vivo data show that genistein utilizes both ERα- and ERβ-mediated mechanisms, depending on the specific tissue, to elicit estrogenic effects on the female mouse reproductive tract. While these models have proven useful in uncovering the effects and mechanism of action of genistein on the mouse reproductive tract, extrapolation of these results to humans has been hampered by conflicting data obtained from epidemiological studies. Therefore, continued efforts to elucidate the biological effects and mechanism of action of genistein are needed, as are further epidemiological studies, to obtain a clearer picture of the beneficial and detrimental effects of genistein exposure in humans.

**METHOXYACETIC ACID**

Methoxyacetic acid (MAA) is the major metabolite of the industrial solvent ethylene glycol monomethyl ether (EGME), used in paints, varnishes, dyes, and fuel additives. Occupational exposure to EGME, and consequently to its major metabolite MAA, have been associated with reproductive toxicity. In women, exposure to ethylene glycol ethers has been associated with increased risk of spontaneous abortion and subfertility, while it is associated with decreased sperm counts in exposed males. 50-56 Laboratory studies have demonstrated that EGME targets the ovarian luteal cell, suppresses cyclicity, and inhibits ovulation in female rats, while in male rats it reduces testicular size and fertility. 57,58 Subsequent studies have established that MAA is responsible for the reproductive toxicities associated with EGME exposure. 53,57

MAA is a member of the short-chain fatty acid family, which includes the antiepileptic drug valproic acid (VPA) and the intestinal bacterial product sodium butyrate (NaB). Interestingly, VPA has also been associated with reproductive toxicities, including menstrual abnormalities and polycystic ovaries. 59-61 One shared feature of MAA, VPA, and NaB is their ability to inhibit histone deacetylases and alter gene expression via histone hyperacetylation. 62-66 However, what role this effect plays in the reproductive toxicities associated with MAA and VPA is unknown.

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Genistein (μg/pup/day)</th>
<th>Lavendustin A (μg/pup/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1</td>
<td>10</td>
</tr>
<tr>
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<td>1/11 (1)</td>
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<td>2/4 (1)</td>
</tr>
<tr>
<td>βERKO</td>
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<td>0/4 (0)</td>
</tr>
</tbody>
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