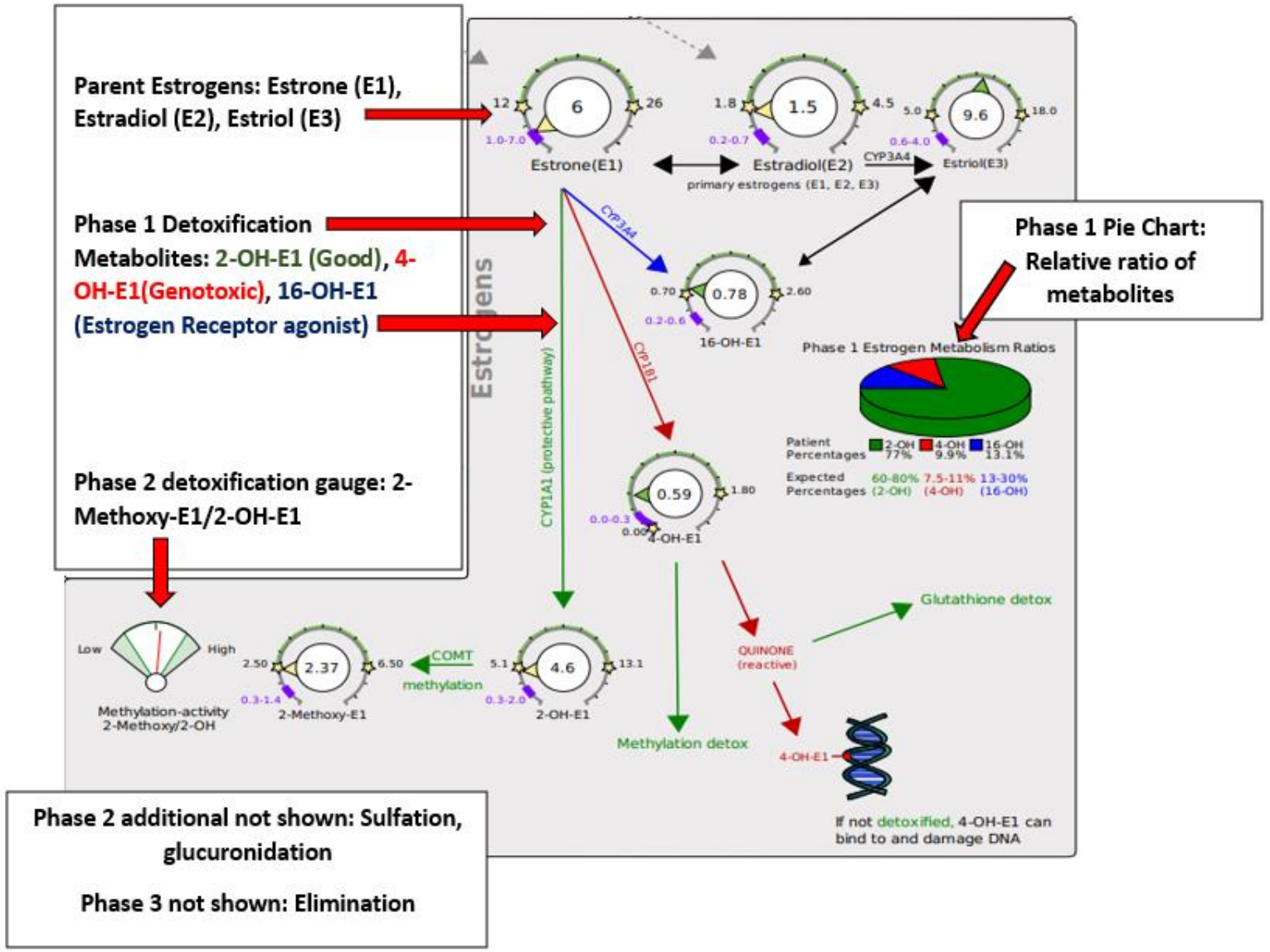
# Estrogen Detoxification

# Estrogen & Its Detoxification

- 3 key phases of detoxification
- Involves proper functioning of liver, stomach, gall bladder, intestines, kidneys, and more!

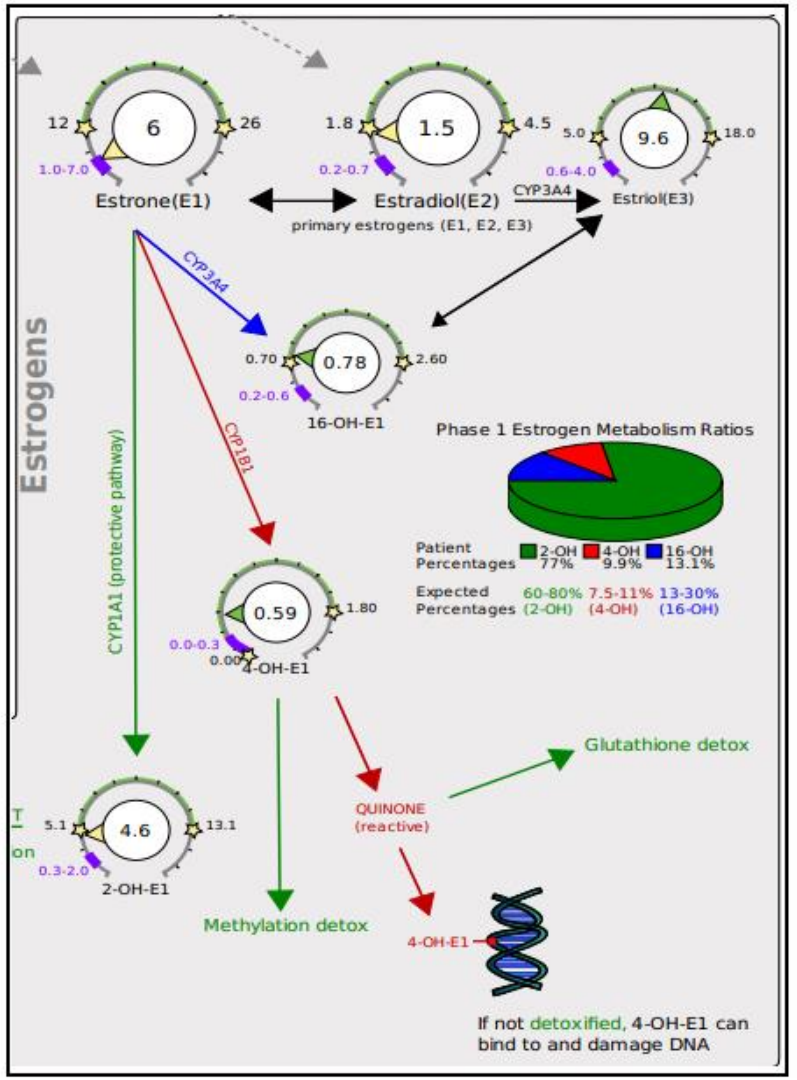


# Phase 1 Detoxification

- The body regularly removes (detoxifies) hormones to regulate the levels.
- Sex hormones are steroid-based hormones (meaning they are built from cholesterol). They are fat-soluble to move through target cells easily.
- Removing hormones requires making them more water-soluble.
- Phase 1 detoxification uses the CYP450 enzyme family to convert estrone and estradiol from a fat-soluble hormone, to a water-soluble hormone.

# Phase 1 Detoxification: Cytochrome Enzyme Systems

- Estrone and estradiol are hydroxylated using CYP 1A1, 1A2, 1B1, and 3A4 enzymes
- Hydroxylation occurs in the liver and peripheral tissues
- Phase 1 creates oxidative intermediates
- Oxidative intermediates are neutralized in phase 2 (methylation, sulfation, glucuronidation)
- Metabolites can still act on E receptors (weakly)
- Genetics + environment influence this process



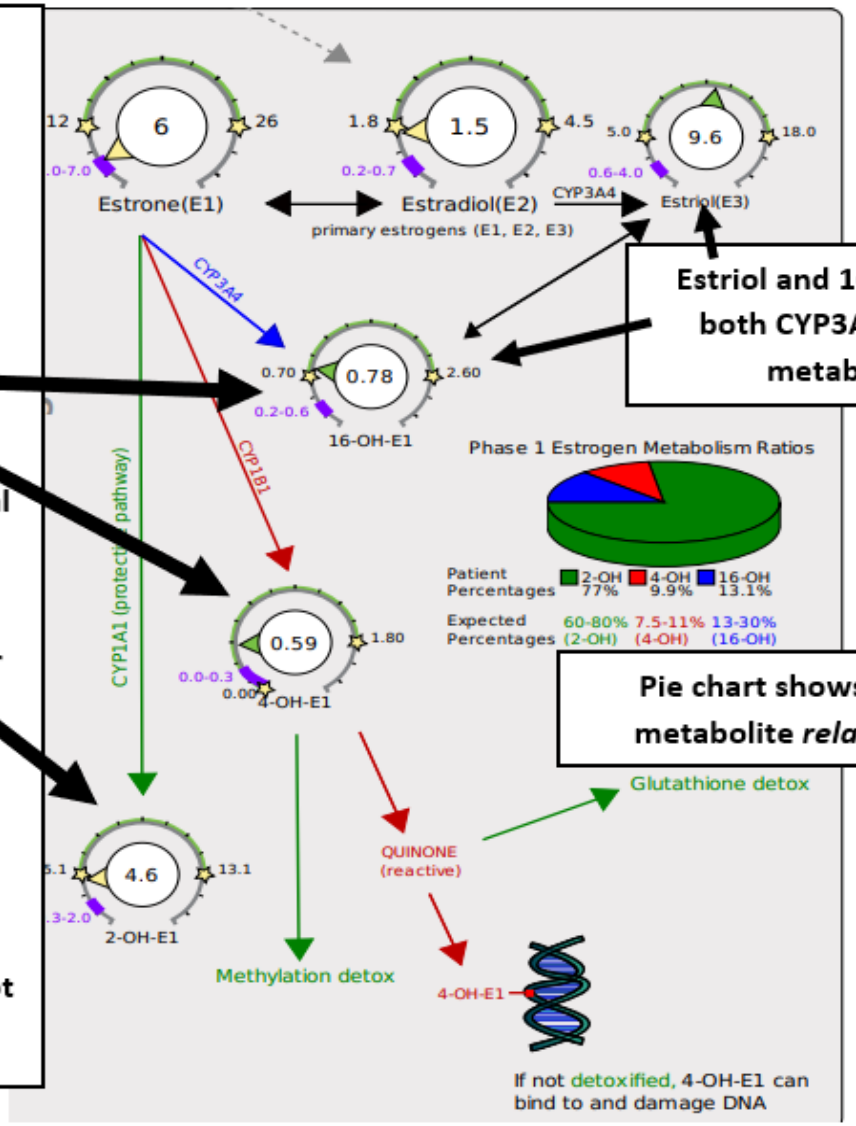
**Phase 1 detoxification metabolites: 2-OH-E1, 4-OH-E1, 16-OH-E1, Estriol**

**16-OH-E1: High estrogen receptor activity**

**4-OH-E1: Least stable metabolite, greatest potential for genotoxicity**

**2-OH-E1: Most stable metabolite, low potential for genotoxicity**

**Other Phase 1 metabolites not shown: 2-OH-E2, 4-OH-E2**




**Estriol and 16-OH-E1 are both CYP3A4 enzyme metabolites**

**Pie chart shows phase 1 metabolite *relative ratio***

# Phase 1 Detoxification: Cytochrome Enzyme Systems

| "2-OH"<br>2-hydroxyestrone &<br>2-hydroxyestradiol | "4-OH"<br>4-hydroxyestrone &<br>4-hydroxyestradiol | "16-OH"<br>16-hydroxyestrone |
|---|---|---|
| CYP1A1 & CYP1A2 | CYP1B1 | CYP3A4 |
| Most stable, least reactive, and most abundant pathway | Potentially genotoxic, most reactive metabolite | Proliferative<br>Can be good for bones, but not so good with breast/fibroids/endo |
| Weakest binding potential to E receptor<br>Anti-proliferative effects on cancer cell lines | If not methylated, it can become the free radical 3,4-quinone which can cause DNA damage | Binds most strongly to estrogen receptor, though still weakly |
| Phase 1: 2, 4, and 16-OH estrogens are oxidative. Phase 2 neutralizes these metabolites. They are also eliminated in urine. | | |

# Phase 2 Detoxification: Methylation, Sulphation, Glucuronidation

- 2-OH & 4-OH catechol estrogens get a methyl group added by catechol-O-methyltransferase (COMT)
- Leads to production of
    - 2- and 4-methoxyestrone
    - 2- and 4-methoxyestradiol
- Conjugation with glucuronic acid and sulfate in liver  more water soluble
- Sulphation & glucuronidation to support excretion thru bile into gut
- Methyl, sulfate, or glucuronide metabolites are neutral and water soluble- easy to excrete!

# Phase 3 Detoxification: Out Of Cells & Into (& Out Of) Gut

- Estrogen glucuronide and sulfate metabolites leave the liver thru bile and are excreted through feces or urine
- B-glucuronidase
  - Removes glucuronide tag, “recycles” estrogen back to active form
  - Found in tissues (ie breast) but also made in the gut by microbiome
  - When made in gut, estrogens can be recirculated rather than excreted, increasing estrogen load
  - Measured on some stool panels
  - Calcium-d-glucurate supplement/in food blocks this enzyme
- Indican can be a marker for gut dysbiosis, and we have seen (in our data) that higher indican correlates with higher estrogen levels

# Phase 3 Detox On The DUTCH Report

Tough to exactly measure, as it's not a urine metabolite

We added indican to our report in 2022 to give insight into gut health.

Data from Precision Analytical samples in postmenopausal women and in men have shown a small, but stastically significant association between elevated urinary indican levels (suggesting dysbiosis) and estradiol levels, reinforcing the assertion that GI dysbiosis is an important factor in circulating estrogen levels.

| Category | Test | | Result | Units | Normal Range |
|---|---|---|---|---|---|
| **Nutritional Organic Acids** | | | | | |
| Vitamin B12 Marker (may be deficient if high) - (Urine) | | | | | |
| | Methylmalonate (MMA) | Above range | 4.89 | ug/mg | 0 - 2.5 |
| Vitamin B6 Markers (may be deficient if high) - (Urine) | | | | | |
| | Xanthurenate | Above range | 1.23 | ug/mg | 0.12 - 1.2 |
| | Kynurenate | Above range | 5.35 | ug/mg | 0.8 - 4.5 |
| Biotin Marker (may be deficient if high) - (Urine) | | | | | |
| | b-Hydroxyisovalerate | Within range | 7.9 | ug/mg | 0 - 12.5 |
| Glutathione Marker (may be deficient if low or high) - (Urine) | | | | | |
| | Pyroglutamate | Below Limit of Detection | 0.0 | ug/mg | 28 - 58 |
| Gut Marker (potential gut putrefaction or dysbiosis if high) - (Urine) | | | | | |
| | Indican | High end of range | 90.4 | ug/mg | 0 - 100 |
| **Neuro-related Markers** | | | | | |
| Dopamine Metabolite - (Urine) | | | | | |
| | Homovanillate (HVA) | Low end of range | 4.4 | ug/mg | 3 - 11 |
| Norepinephrine/Epinephrine Metabolite - (Urine) | | | | | |
| | Vanilmandelate (VMA) | Above range | 7.3 | ug/mg | 2.2 - 5.5 |
| Neuroinflammation Marker - (Urine) | | | | | |
| | Quinolinate | Above range | 13.2 | ug/mg | 0 - 9.6 |
| **Additional Markers** | | | | | |
| Melatonin (*measured as 6-OH-Melatonin-Sulfate) - (Urine) | | | | | |
| | Melatonin* (Waking) | Below range | 1.3 | ng/mg | 10 - 85 |
| Oxidative Stress / DNA Damage, measured as 8-Hydroxy-2-deoxyguanosine (8-OHdG) - (Urine) | | | | | |
| | 8-OHdG (Waking) | Within range | 3.8 | ng/mg | 0 - 5.2 |

# Summary

| | Phase 1: CYP Enzyme detox | Phase 2: Neutralization & water solubility | Phase 3: Excretion |
|---|---|---|---|
| Key steps | CYP enzymes convert estradiol into 3 main metabolites, 2-OH, 4-OH, 16-OH (which are oxidative!) | Methylation, glucuronidation, & sulfation stabilize and are easily excreted | Excretion out of liver cells and into bile to feces/urine (hopefully no excess B-glucuronidase and no excess reabsorption!) |
| Potential signs of a problem | Excess relative production of 4-OH or 16-OH metabolites | Poor methylation, slow COMT, high B-glucuronidase | Dysbiosis, slow bowel movements, dehydration, high estrogen |
| How to help | Ensure liver function<br>**Requires** Iron<br>+DIM, I3C, quercetin, sulforaphane | Phase 2 support includes B6, B12, folate, methionine, choline, TMG, sulfation support<br>Genetic snps and nutrient deficiency may inhibit | Improve the microbiome<br>BM daily<br>Ensure stomach acid<br>Increase water, fiber<br>+ Prebiotics, Calcium D glucarate<br>Unpeeled, raw carrots<br>**AVOID:** antibiotics, junk food, alcohol |

# Clinical Impact Of Impaired Metabolism After Menopause

- Clinical impact is lower in menopause because estrogen and metabolites are very low
- HRT increases estrogens and therefore clinical impact of detox
- **Phase 1:**
  - 16-OH like estrone in ER receptor activity
  - Higher 16-OH associated with lower osteopenia
  - Higher 16-OH associated with higher *recurrence* of breast cancer in survivors
  - Higher 4-OH remains genotoxic, but levels are very low- impact not clear
- **Phase 2:**
  - Not well understood when estrogens are so low
  - Implies nutrient deficiency or suboptimal lifestyle which have other health implications

# Estrogen Detox in Menopause

- Estrogen detox pathways are the same in menopause
- The clinical impact is not well understood when estrogen is this low
- HRT increases the detox load
- Maintaining healthy detox is relevant, especially with HRT
- Support all phases: Liver, gallbladder, methylation, hydration, bowel transit time, gut microbiome

# Thank You!

If you are interested in learning more about hormones, each week we hold one-hour long mentorship sessions! Once you are a registered DUTCH provider, you can book these through our online scheduling link. Please call to get registered today.

**For questions, contact:**

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