Global/Local Electrophilicity as Measure of Endocrine Disruptor Genotoxicity

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ABSTRACT

Exogenous endocrine disrupting chemicals (EDCs) bind to nuclear hormone receptors and are implicated in hormone-sensitive cancer development. Reactive metabolites of some EDCs form stable and depurinating adducts with DNA [1, 2] with the key step of adduct formation being a 1,4-Michael addition between a nucleophile (DNA) and electrophile (EDC) [3]. To evaluate potential genotoxicity of neutral EDC metabolites, we employ a conceptual DFT study (B3LYP-D3BJ/ def2-TZVPD) to evaluate their global electrophilicity values via:

$$\omega \equiv \mu^2/2\eta \text{ where } \mu = (\partial E/\partial N)_{v(r)} \text{ and } \eta = (\partial^2 E/\partial N^2)_{v(r)} \quad (1)$$

We discover that many estrogenic EDC metabolites have comparable global electrophilicity values to endogenous, reactive estrogen quinone metabolites (see Fig. 1). We evaluate local electrophilicity using a Fukui function approach to identify potential covalent bond formation sites. Our classical and quantum mechanics/molecular molecular dynamics simulations show barrierless approach of metabolites into minor and major DNA grooves under biological conditions.

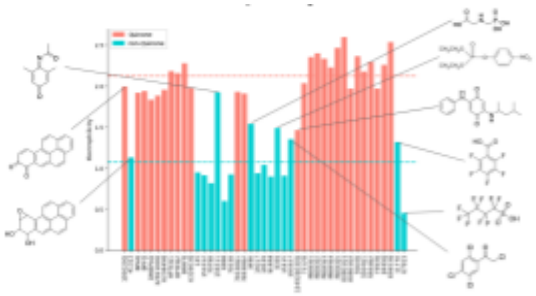

Figure 1: Global electrophilicity values of selected quinone and non-quinone metabolites of known EDCs (several 2D metabolite structures shown on sides).

References

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