Single vs. Multiple Target Organ Identification in Target-Organ-Specific Hazard Index (TOSHI) Chemical Mixture Risk Assessment

US EPA guidance for evaluating non-cancer hazards in risk assessment of chemical mixtures recommends identifying substance-specific target organs to calculate a target-organ-specific hazard index (TOSHI). Because of the general lack of mode of action (MoA) and pharmacokinetic information, target organ identification (TOI) is often used to approximate toxicological similarity among different substances. Although no explicit protocol for TOI exists, the target organ for a particular chemical can be identified from the critical effect in the principal study chosen as the basis for the corresponding toxicity reference value used in the risk assessment underway (e.g., the basis for an EPA IRIS value). Designating a single target organ for chemicals when multiple target organs are indicated in this basis for the reference value (e.g., trichloroethylene, ethylbenzene) may add substantial uncertainty to the risk assessment and ultimately underestimate risk. Our analysis of hazard indices (HIs) for a select group of chemicals in a simulated chemical mixture risk assessment compared traditional summation HI values, TOSHI values for a single target organ, and TOSHI values for multiple target organs. Our analysis revealed that, for these chemicals, multiple target organ TOSHI values are more conservative (i.e., closer to a hazard quotient of 1) than single organ TOSHIs, but slightly lower than HI summation values across all substances with no consideration of toxicological similarity. Although all three methods contain assumptions and uncertainties, we conclude that, for the selected chemicals, multiple target organ TOSHI analysis provides a sufficiently health-protective value that also considers substances' potential to preferentially affect more than one target organ. We discuss other key considerations and uncertainties that affect TOSHI derivation in chemical mixture risk assessment, including TOI for systemic/generic effects (e.g., decreased bodyweight), using developmental or reproductive categories as their own "target organs," and high dose effects as they relate (or not) to a substance's MoA at plausible exposure levels.