NICEATM/ECVAM/JaCVAM Multi-phased International Validation Study of a Stably-Transfected Estrogen Receptor (ER) Transcriptional Activation (TA) Test Method.

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The U.S. EPA proposed Tier 1 endocrine disruptor screening program (EDSP) includes validated *in vitro* test methods to determine if chemicals bind to the ER. A stably transfected ER TA method (LUMI-CELL®, Xenobiotic Detection Systems, Inc.) to detect ER agonists and antagonists was subsequently nominated to the Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM) and recommended for validation studies. NICEATM, ECVAM, and JaCVAM designed and initiated a four phase international validation study to evaluate the reproducibility and accuracy of the LUMI-CELL® ER bioassay. The study is using three laboratories, one each in Japan, the U.S., and Europe. A standardized test method protocol incorporating ICCVAM recommended ER TA essential test method components is being used to evaluate 78 coded reference substances recommended by ICCVAM for validation of *in vitro* ER test methods. The first phase will evaluate positive and vehicle controls and establish test acceptance standards for each laboratory. The second phase will evaluate 12 coded reference substances in each lab in two stages. Intra- and inter laboratory reproducibility and accuracy will be assessed during and after each of the first two phases. Excessive variation and discordance will be investigated and protocols modified accordingly. The third phase will evaluate the performance of the optimized test method protocol using the remaining coded 41 minimum validation substances. The final phase will test the final 25 substances in one laboratory. Performance standards will be developed to serve as the basis for determining if similar ER TA methods have comparable or better performance. This multi-phased approach is expected to identify and resolve sources of variation early in the validation process and to generate a highly reproducible test method protocol for international regulatory use. Supported by NIEHS Contract N01-ES-85424.

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