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Validation Status of the Isolated Rabbit Eye (IRE) Test Method

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Concerns about animal welfare and interest in higher throughput testing have led to the development of alternatives to the current rabbit eye test. NICEATM evaluated four *in vitro* ocular test methods for their ability to identify irreversible or severe irritants/corrosives as alternatives to the rabbit eye test. One of these test methods, IRE, is an organotypic model that maintains normal physiological and biochemical function of the isolated eye. The ability of IRE to correctly identify ocular corrosives/severe irritants using available IRE and corresponding *in vivo* irritation data was evaluated according to current hazard classification schemes defined by the U.S. EPA (n=77), the European Union (n=149), and the UN Globally Harmonized System (n=81); accuracy (48-86%), and false positive (22-59%)/false negative (0-57%) rates varied widely but consistently across regulatory systems. When fluorescein retention and/or epithelial integrity assessment were included (EU system only; n=65), accuracy was 77-86%; false positive and false negative rates were 23-34% and 0%, respectively. Lack of published intra- and interlaboratory data for this assay version precluded an evaluation of reliability. A proposed standardized test method protocol and a proposed recommended list of reference substances have been developed for future validation/testing studies to further assess the accuracy, reliability, and the applicability domain of IRE for the detection of ocular corrosives/severe irritants. IRE may be useful in a tiered testing strategy where positive results can be used to classify and label a substance, while substances with negative results would undergo additional testing to identify false negative ocular corrosives/severe irritants and to identify those chemicals with reversible ocular effects. This approach would reduce the number of animals used for eye irritation testing and reduce the number of animals experiencing pain and distress. ILS staff supported by NIEHS contract N01-ES 35504.

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