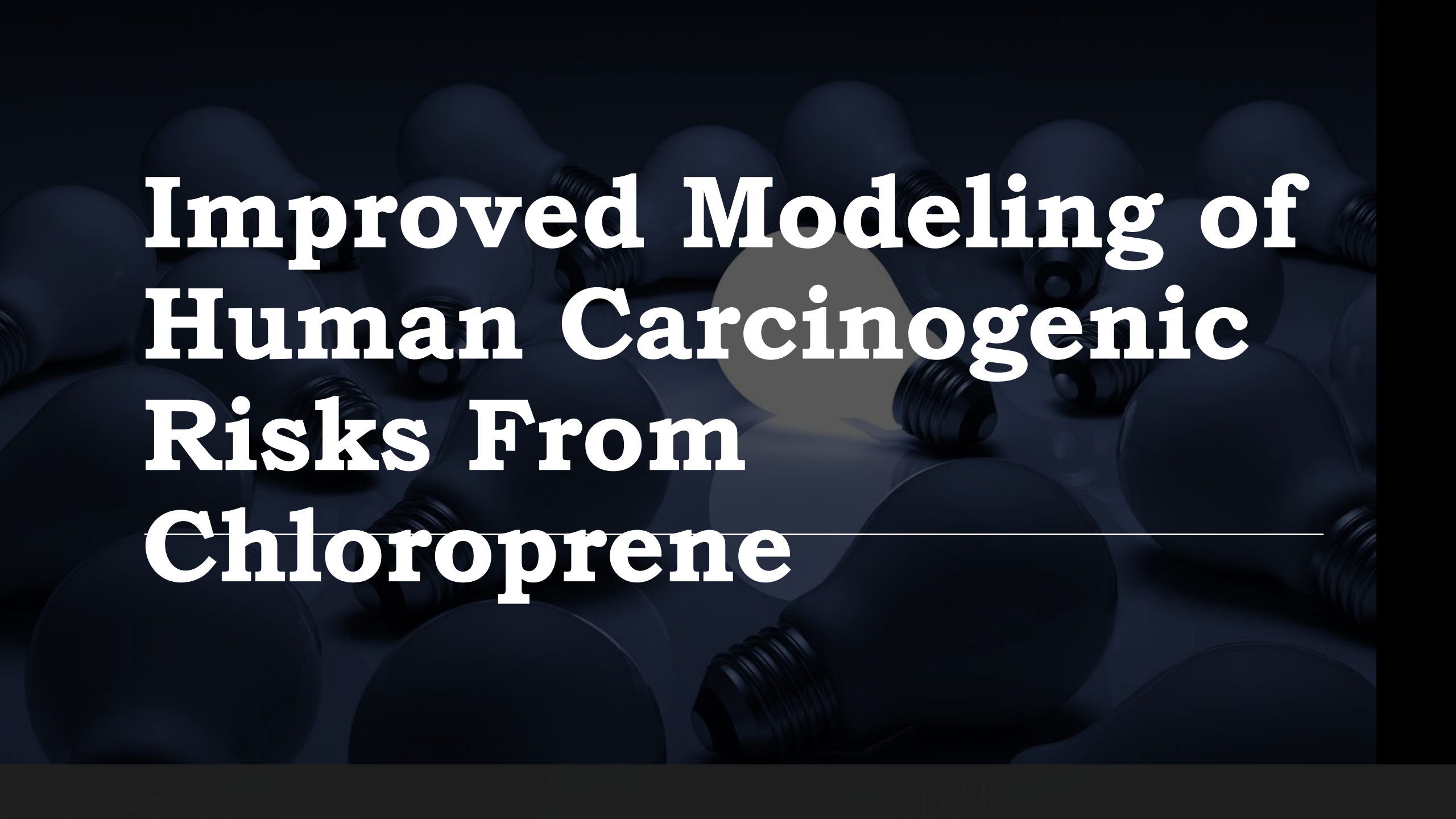

Improved Modeling of Human Carcinogenic Risks From Chloroprene

Key Issues

Dosimeter for Interspecies Projection of Cancer Risk

--Should not just be just the gross production of active metabolite

--Should be the internal concentration X time of active metabolite.

(recognizing the likely slower metabolic destruction of the active metabolite(s) in people compared to rodents)

Projection of Risk When Multiple Modes of Action Act Together

Construction and Calibration of the PBPK Model

Appropriate Analysis of Uncertainty

Dosimeter for Interspecies Projection of Cancer Risks

The appropriate dosimeter depends on the fundamental mode of action. For carcinogenesis via DNA reacting carcinogens, this is mutagenesis related to reaction with DNA and a failure to completely repair/reverse the reaction before the DNA is next copied. Copying of the reacted DNA is when the change can be effectively “fixed” into the genome.

Projection of Risk When Multiple Modes of Action Act Together

It often happens that an effect with a low-dose linear mode of action (e.g. mutagenesis via direct DNA reaction) is accompanied by effects that occur via other modes of action. For example a low dose linear effect can be accompanied by an adverse effect that occurs via an upward turning dose response relationships from a traditional toxic mode of action (e.g., gross overwhelming of some homeostatic process. When effects with low-dose linear relationships are present in the same system as upward-turning nonlinear relationships, basic math indicates that the low dose linear relationships will tend to dominate at the limit of low dosage.

Construction and Calibration of the PBPK Model

Optimal Conditions (e.g. Ph, Cofactor Concentrations) for Measuring Enzyme Activities do not Always Correspond to the Conditions Where Enzymes Must Act In Vivo

So Enzyme Parameters Derived from In Vitro Measurements do Not Always Accurately Reflect In Vivo Activity. Reliable Calibration of Adjustable Parameters Should, if at All Possible, Reflect in the Results of In Vivo Exposures.

PBPK Modeling Can Potentially Enhance Risk Analysis, But Must Be Used with Care, and Critical Evaluation