(IIIE-1) Dose-Response Modeling for the Assessment of Cumulative Risk Due to Exposure to *N*-Methyl Carbamate Pesticides

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The US EPA's *N*-Methyl Carbamate Cumulative Risk Assessment (NMCRA) assesses the effect on acetylcholine esterase (AChE) activity of exposure to 10 *N*-methyl carbamate (NMC) pesticides through dietary, drinking water, and residential exposures. Similarly to the Agency's organophosphate cumulative risk assessment, the NMCRA is based on the relative potency factor (RPF) approach; however, unlike organophosphate-induced AChE inhibition, NMC inhibition is short-lived, with half-lives on the order of hours, rather than days. Thus, the risk assessment for NMC pesticides needs to take account not only peak AChE inhibition but the recovery of inhibition after exposure. This information was estimated from animal studies using dose-time-response modeling of gavage studies. As there were multiple data sets for each chemical, statistical methodology was used that allowed all the data to contribute to the overall dose-response estimate. Relative potencies were calculated as the ratios of benchmark doses for 10% AChE inhibition. The half-life for recovery of AChE activity was estimated simultaneously with BMDs. In addition to the rat data, there was also red-blood cell AChE inhibition data for three chemicals in humans. A Bayesian analysis of the ratio of BMDs in rats to that in humans provided some information about ranges of animal to human uncertainty factors that are consistent with the dose-response data, both for the chemicals for which there is human data and (making a strong assumption about the distribution of animal to human potency ratios among the *N*-methyl carbamates) among the carbamates for which there are no human data. These data thus inform, but do not completely determine, the uncertainty factors actually used in the risk assessment. After completing the dose-response modeling for the individual chemicals, it became clear that dose-response shapes for the NMCs were not all perfectly consistent with the RPF approach. An analysis of the more general characterization of dose-additivity, however, shows that for the MOE approach used in this risk assessment, the conclusions of the risk assessment would not be affected had the more general formulation been used. *[Although this work was reviewed by EPA and approved for publication, it may not necessarily reflect official Agency policy.]*