April 21, 2021

Annie M. Jarabeck
Office of Research and Development
Environmental Protection Agency
1200 Pennsylvania Ave. NW
Washington, DC 20460-0001
via regulations.gov

Re: Comments on Multiple-Path Particle Dosimetry (MPPD) Model Software (MPPD EPA 2021 v.1.01) With Technical Support Documentation and User's Guide (External Review Draft), EPA-HQ-ORD-2020-0564; 86 FR 15476 (March 23, 2021)

Dear Ms. Jarabeck:

Established in 1933, CropLife America (CLA) represents the developers, manufacturers, formulators, and distributors of pesticides and plant science solutions for agriculture and pest management in the United States. CLA represents the interests of its registrant member companies by, among other things, monitoring legislation, federal agency regulations and actions, and litigation that impact the crop protection and pest control industries and participating in such actions when appropriate. CLA's member companies produce, sell, and distribute virtually all the pesticide and biotechnology products used by American farmers.

CLA appreciates the opportunity to comment on the Environmental Protection Agency (EPA or Agency) Multiple-Path Particle Dosimetry (MPPD) Model and Software with Technical Support Documentation and User's Guide (MPPD EPA 2021 v.1.01). The development and publication of this technical document, and its future implementation across EPA would lead to significant advancements in the conduct of human inhalation risk assessments.

The EPA Office of Pesticide Programs (OPP) currently employs Regional Deposited Dose Ratio (RDDR) for rat-to-human dosimetry in inhalation risk assessments supporting pesticide registrations. While this tool was state-of-the-art when adopted, it no longer provides the best option for dosimetric adjustments. Adoption of MPPD as an acceptable tool for dosimetry and agreement on best practices for parameterization of the model will progress dosimetric practices to allow for greater human-relevance and compatibility with non-animal methods of toxicity testing. The following specific benefits of the MPPD model will result in improved inhalation risk assessments for pesticide handlers:

- ***Ability to model different particle size distributions for test species and humans****:* Current practice for rat-to-human dosimetry assumes that both the test species and humans are exposed to particles with the size characteristics of the aerosols used in rodent toxicity studies. As real-world exposure for humans can differ significantly from the small, respirable particle ranges used for rodent studies, this approach can result in unrealistic predictions for human particle deposition and distribution throughout the airway. The ability to model exposures separately for the test species and humans will result in dosimetric conversions that are more accurate and relevant to exposure assessments.
- ***Greater range of particle sizes****:* MPPD is capable of modeling exposures to particles up to 100 µm; pesticide handler exposure models currently employed are based on a set

of generic handler exposure data, where the inhalation exposures were estimated using samplers designed to collect inhalable components in the air. As RDDR can only accommodate aerosols up to 30 µm, it may not appropriately model exposures to pesticide sprays, which tend to have larger median particle sizes. Adoption of MPPD will allow for risk assessments that are more relevant to real-world exposure conditions.

- ***Incorporation of various breathing rates and patterns, clearance rates, and inhalability adjustment****:* Breathing rate and breathing pattern (nose-breathing, mouth-breathing, or hybrid breathing) may vary depending on the handler activities. The ability to modify breathing rates while including clearance and inhalability adjustment in MPPD will allow for refinement of risk assessments for exposures while performing specific tasks, such that the breathing rates and patterns reflect those typical of the level of exertion involved in performing the task.
- ***Compatibility with current operating systems****:* As RDDR was designed to run in a Disk Operating System and has not been updated, it can be difficult to run on current computers. The compatibility of MPPD with current operating systems makes it more broadly accessible and will increase transparency in Agency risk assessments as registrants will be more readily able to conduct their own dosimetric conversions and understand how these were done in Agency assessments.
- ***Adoption of non-animal methods for toxicity testing****:* The ability to model species-specific regional deposited dose using MPPD allows its use in support of *In vitro* to *In vivo* extrapolation. This will be critical as we move toward the Agency's goal to eliminate animal testing by 2035.

Overall, the development of this technical support document and user's guide will be an important step toward modernizing inhalation dosimetric approaches to be more transparent, more relevant to the human exposures of concern, and more compatible with non-animal approaches to estimating hazard. CLA commends EPA on this effort and looks forward to implementation of MPPD in future Agency risk assessments.

CLA appreciates the opportunity to comment on the MPPD User Guide**.** Should you have any questions or comments, please feel free to contact me at mbasu@croplifeamerica.org or (202) 296-1585.

Sincerely,

Manojit Basu

Managing Director, Science Policy

CropLife America