August 14, 2018

Office of the Science Adviser
Environmental Protection Agency
1200 Pennsylvania Avenue, NW
Washington, DC 20460

Re: Docket No. EPA-HQ-OA-2018-0259

Dear Sir:

The Halogenated Solvents Industry Alliance, Inc. (HSIA) is pleased to have the opportunity to offer these additional comments on EPA's proposed rule to strengthen transparency in regulatory science. 83 Fed. Reg. 18768 (April 30, 2018). The intent of this rule is to ensure that EPA uses scientific information in its assessments that is publicly available to allow for independent validation, particularly when the scientific studies are pivotal to regulatory action. HSIA represents producers and users of trichloroethylene, perchloroethylene, methylene chloride, and carbon tetrachloride. All four of these chemicals have been reviewed by EPA for its Integrated Risk Information System (IRIS) and they are all priorities for risk evaluation under the Toxic Substances Control Act (TSCA), as amended by the Frank R. Lautenberg Chemical Safety for the 21st Century Act. In the IRIS assessments for these chemicals, EPA used the default low-dose linear approach for estimating cancer risks with assumptions that were not entirely transparent, and which were inconsistent with available epidemiology and mode of action (MOA) data.

HSIA fully supports requiring cancer risk assessments to evaluate the appropriateness of assuming a linear non-threshold dose-response model on a case-by-case basis. EPA points out in its *Guidelines for Carcinogen Risk Assessment* (2005):[1]

> "When risk assessments are performed using only one set of procedures, it may be difficult for risk managers to determine how much health protectiveness is built into a particular hazard determination or risk characterization. When there are alternative procedures having significant biological support, the Agency encourages assessments to be performed using these alternative procedures, if feasible, in order to shed light on the uncertainties in the assessment, recognizing that the Agency may decide to give greater weight to one set of procedures than another in a specific assessment or management decision."

The overreliance on the linear non-threshold dose-response model by EPA as the default approach to assessing cancer risk without also considering alternative non-linear models obscures a cascade of

[1] EPA, Guidelines for Carcinogen Risk Assessment, EPA/630/P-03/001F (2005).

underlying conservative assumptions in the linear dose-response model. There have been considerable advances in scientific understanding of the MOAs and mechanisms for a particular carcinogenic response, with some MOAs supporting a non-linear (threshold) approach to dose response. Thus, determining the appropriateness of a model for extrapolating the dose-response of a carcinogenic effect of a chemical also entails an evaluation of the hypothesized carcinogenic MOAs. A systematic approach, such as the procedure developed by Becker *et al.* (2017),[2] which enables side-by side comparison of numerical weight of evidence confidence scores for different hypothesized MOAs, would enhance the transparency of the selection of the dose-response models to be used in assessing cancer risk.

HSIA also endorses efforts by EPA to improve the public availability of the dose-response models used in its assessments for the purpose of independent validation. Our experience with EPA's physiologically-based pharmacokinetic (PBPK) model for TCE indicates that replication of this model poses difficulties for even sophisticated users, based on the level of documentation that is currently available to the public in the IRIS Toxicological Review for TCE. Thus, EPA is encouraged to develop a system by which the same models that EPA uses in its risk assessments can also be used by the public for independent validation efforts.

Respectfully submitted,

Faye Graul/WCN

Faye Graul
Executive Director

[2] Becker, R.A., Dellarco, V., Seed, J., Kronenberg, J.M., Meek, B., Foreman, J., Palermo, C., Kirman, C., Linkov, I., Schoeny, R., Dourson, M., Pottenger, L.H., and Manibusan, M.K., Quantitative weight of evidence to assess confidence in potential modes of action, Regul. Toxicol. Pharmacol. 86: 205-220 (2017).