

Charge Questions for June, 2020 Science Advisory Board

New Approach Methods and Reducing the Use of Laboratory Animals for Chronic and Carcinogenicity Testing

In accordance with the September, 2019 directive from EPA Administrator Andrew Wheeler, EPA's Office of Pesticide Programs (OPP) and Office of Pollution Prevention and Toxics (OPPT) are working to reduce the number of laboratory animal studies requested or required for pesticides and industrial chemicals. Beyond the ethical issues associated with animal use, new approach methods (NAMs) are expected to improve the scientific foundation of risk assessments by providing human-relevant information that is more efficient and less costly. In collaboration with the Office of Research and Development and multiple stakeholders, EPA-OCSPP has developed a draft white paper highlighting three projects that are improving the science used in risk assessment for chronic/carcinogenicity testing. These activities are organized by the 3Rs principles for laboratory animal testing-- *reduce, replace, refine* as originally proposed by Russell and Burch (1). Because of the complexities in biology and toxicology, there will not be a "one-size-fits-all" solution to improving chronic/carcinogenicity testing. As such, EPA and its collaborators are taking a multifaceted approach that advances several areas simultaneously. The agency requests the SAB provide comment on the following charge questions.

1. EPA-OPP is participating in the Rethinking Carcinogenicity Assessment for Agrochemicals Project (ReCAAP) with government, non-governmental organization, and industry stakeholders (Section 2). ReCAAP is developing a risk-based weight of evidence (WOE) approach for waiving chronic and carcinogenicity studies. This proposed approach is consistent with existing guidance¹ and current practice² for other types of toxicology studies.
 - a. Please comment on the draft risk-based WOE approach for waiving chronic/carcinogenicity studies (Attachment 1). Please include in your comments a discussion of the clarity and completeness of the proposal.
 - b. Please comment on the draft case study provided (Attachment 2). Please include in your comments a discussion of the clarity and completeness of the proposal.
2. EPA is collaborating with Division of the National Toxicology Program (DNTP) of National Institute of Environmental Health Sciences (NIEHS) and HESI to consider NAM-based approaches to begin to replace the chronic/carcinogenicity testing in mammals. In addition, EPA-OPP and ORD are working together to collect quantitative gene expression data from short-term *in vivo* rat studies for a selected set of pesticides that cause liver tumors in rodent with known modes of action. All of these efforts are in the early stages of development and would benefit from expert and public input.

¹ <https://www.epa.gov/sites/production/files/2015-04/documents/data-require-guide-principle.pdf> ;
<https://www.epa.gov/sites/production/files/2014-02/documents/part158-tox-data-requirement.pdf>

² Craig et al (2019) Reducing the Need for Animal Testing While Increasing Efficiency in a Pesticide Regulatory Setting: Lessons From the EPA Office of Pesticide Programs' Hazard and Science Policy Council. Regul Toxicol Pharmacol, 108, 104481 Nov 2019. PMID: 31546018

- a. Please comment on the direction and scope of the three collaborative projects described in Section 3 of the draft white paper.
3. EPA is working with HESI, NTP, and other government and industry stakeholders to accelerate the incorporation of kinetically-derived maximum doses (KMD) into repeat dosing studies like the chronic/carcinogenicity study as an alternative to the traditional maximum tolerated dose (MTD). The KMD approach is consistent with numerous guidance documents developed by EPA, OECD and other international organizations as a more humane and human relevant approach to dose selection. One KMD study has been provided to the SAB along with the description and agenda of an upcoming workshop and the scope/charge of a workgroup at HESI to develop additional case study and a best practices document.
 - a. Please comment on EPA's current KMD-related activities as described in Section 4 and Attachments 3 and 4. Does the SAB have additional activities that EPA could consider?