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To: Federal Task Force on Research Specific to Pregnant Women and Lactating Women (PRGLAC)

via email to Lisa Kaeser, JD, Executive Secretary, kaeserl@mail.nih.gov

The Teratology Society respectfully submits the following comments to the Task Force on Research Specific to Pregnant Women and Lactating Women (PRGLAC) for consideration and in fulfilling its task to identify gaps in knowledge and research on safe and effective therapies for pregnant women and lactating women.

The Teratology Society is an international, nonprofit organization consisting of researchers, clinicians, epidemiologists, and public health professionals from academia, government, and industry. Together, our mission is to prevent birth defects and disorders of developmental origin by promoting research and exchange of ideas, communicating information to health professionals and other interested parties, and providing education and training. We are committed to supporting new research initiatives that address questions regarding exposures to pregnant and breastfeeding women and defining associated risks; rapidly assessing and integrating new information on research results into the information we provide to women, health care providers and the general public; and communicating with these populations through our website (www.teratology.org), publications, position papers, blogs, and social media campaigns. Our journal, *Birth Defects Research*, publishes original scientific research that contributes to the understanding of the biology of embryonic development and the causative factors and mechanisms leading to adverse pregnancy outcomes.

As noted in the statement presented by Kathy Wisner, M.D., the Teratology Society joins with OTIS (Organization of Teratology Informational Services/ Mother to Baby) in applauding the PRGLAC effort, which aligns well with our mission and strategic goals. Here, we are providing additional comment, reflecting the breadth and depth of experience of our members, who include leaders in the fields relevant to the topics being addressed by the Task Force. The Teratology Society fully endorses the concept that pregnant or breastfeeding

women need access to translatable information on medications in order to be able to make informed choices regarding their health and the health of their child.

The evaluation of potential developmental and reproductive risks of new drugs continues to rely on nonclinical testing in animals, as it is the only integrated model for pregnancy that takes into account both maternal and fetal environments. While these studies have proven invaluable to informing health care providers, policy makers/regulators, and patients of potential risks, there remains a critical need for improved nonclinical models (e.g., lactation) and basic developmental, mechanistic and computational research to improve translational understanding. The Teratology Society endorses the statement previously provided by the ILSI Health and Environmental Sciences Institute (HESI) Developmental and Reproductive Toxicology (DART) Technical Committee regarding the importance of robust nonclinical research to support improved clinical development of safe and effective therapies for pregnant and lactating women. Advances in nonclinical research and translation to clinical outcomes is a prominent theme of the Teratology Society annual meeting, position papers, and other communications, where the diverse perspectives of our multidisciplinary membership provide a robust and comprehensive evaluation of these topics.

The need for systematic research on the safety of medicines used during pregnancy and lactation to provide relevant data to women for making informed health care decisions is clear. Yet, as highlighted in the November 6 - 7, 2017 PRGLAC meeting, the inclusion of pregnant and lactating women in clinical trials continues to present numerous ethical challenges, including the need for maternal treatment in the face of potential fetal/infant risk, and thus faces ongoing general reluctance. The Teratology Society commends the PRGLAC for their much-needed attention to this topic and supports ongoing discussion and consideration of approaches for the safe and meaningful study of drugs in pregnancy and lactation. We believe that the Teratology Society, as a multidisciplinary organization, is in a unique position to contribute to this discussion.

Central to the mission of the Teratology Society is the communication of information to health professionals, investigators, policy makers and other interested parties. We recognize that the development of an effective communication strategy designed to provide information to various audiences with differing interests, backgrounds, and understanding can be challenging. When developing messages related to use of medicines in pregnancy and lactation, it is critical that considerations for the therapeutic benefit of the medicine, the potential risk of the untreated maternal disease state to the woman and/or child, as well as for potential risks of the medicine, are balanced. Messages must be uniquely crafted and disseminated through a variety of channels to reach and inform health care providers, patients, and the general public, as well as policy makers, to enable their ability to make informed decisions. Language, cultural aspects, socio-economic status, and level of education must be considered in outreach efforts. Redundant delivery of the message in multiple formats can help ensure dissemination, comprehension, and impact. The use of communication partnerships, such as the collaboration that the Teratology Society has with OTIS, can be instrumental in effective implementation of communication strategies, and in maintaining their relevance in a rapidly evolving scientific and social environment.

The success of communication efforts also needs to be reassessed and adjusted regularly. The FDA Pregnancy and Lactation Labelling Rule (PLLR; <https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/Labeling/ucm093307.htm>) is a prime example of such communication adjustment. The PLLR requires changes to the content and format of information presented in prescription drug labeling in order to assist health care providers in assessing benefit versus risk and in subsequent counseling of pregnant women and nursing mothers who need to take medication, thereby allowing them to make informed and educated decisions for themselves and their children.

Finally, with regard to research needs to advance clinical knowledge for pregnant and lactating women, it is clear that no single approach will solve this issue. Continued advances in nonclinical research to improve our mechanistic understanding of development, and translation of animal studies will continue to strengthen our confidence in predicting and communicating potential risks associated with use of drugs in pregnancy and lactation. Of particular note is a need for improved nonclinical models for lactation. In addition, concern for fetal risk has largely focused on structural outcomes resulting from early pregnancy exposure. A greater understanding of risk throughout pregnancy, as exemplified by divergent outcomes associated with Zika virus, is a critical need. A judicious approach is needed for the conduct of clinical trials in pregnant and lactating women to provide meaningful data for the appropriate use of therapies in pregnancy and lactation. Effective approaches for identification, collation, and communication of data from other available sources (e.g., post-marketing reports, case studies) are needed, and consideration should also be given to post-approval observational studies.

The Teratology Society endorses continuous and rigorous support for the scientific and methodological research that underpins the availability of safe and effective therapies in pregnant women and lactating women, as well as health and risk communication efforts. The multidisciplinary nature of such research is embedded in the Teratology Society mission and strategic goals.

We again thank the PRGLAC Task Force for the opportunity to provide comments and encourage the Task Force to take these points into consideration in your final report.

Sincerely,

Teratology Society