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Comments to the External Peer Review Meeting for Report on Physiologically Based Pharmacokinetic (PBPK) Modeling for Chloroprene (Ramboll, 2020) and a Supplemental Analysis of Metabolite Clearance (U.S. EPA, 2020), October 4-5, 2020

85 Fed. Reg. 44,885 (July 24, 2020), Docket: EPA-HQ-ORD-2020-0181-0001

The published chloroprene PBPK model of Yang et al. (2012) used in vitro data and in vitro to in vivo extrapolation (or IVIVE) calculations to estimate metabolic rates in both the liver and lung of humans. However, due to the uncertainty in the available in vitro data for the human lung, Ramboll (2020) proposed use of read-across in vitro data for 7-ethoxycoumarin, estimated from microsomes derived from 12 human tissue donors to estimate average metabolic activity across the adult human population. The 12 samples are described in the Lorenz (1984) paper only by age and sex, 3 females and 9 males, ranging in age from 32 to 81. No race, ethnicity or other information is provided, though since all authors are German it is reasonable to presume that the geographic distribution is contained within Germany. Clearly, 3 German women aged 39 and over do not represent the diverse National population, and even less so the populations of St. John the Baptist and St. Charles, the communities that surround the Denka chloroprene manufacturing facility, and have the highest cancer risks in the country from air pollution, driven largely by chloroprene emissions from Denka.

The Agency should be very cautious about using the in vitro to in vivo extrapolation (or IVIVE) approaches. The IVIVE approach that hasn't been applied to IRIS before. In his comments to this panel on behalf of Ramboll consultants, Dr. Harvey Clewell stated that it is used by the EPA Pesticide Office for early life sensitivity, but this isn't quite accurate. It was just sent to a peer review panel a few weeks ago (Ken Portier, Ray Yang and Harvey Clewell all served on that panel as well). In fact, the IVIVE approaches utilized by the EPA Pesticide Office suffer from significant limitations. First, the Administered Equivalent Doses (AEDs) derived from the IVIVE calculations were often several orders of magnitude higher than the BMDL10 estimates – which in some cases (e.g., chlorpyrifos) are known to be underestimates of the levels that cause harm in children. The Pesticide Office white paper says the reason for AEDs exceeding the BMDL10s is that the IVIVE calculations were based upon the median individual in the general population. This is a completely unacceptable model assumption for no-safe-dose health endpoints like developmental neurotoxicity and carcinogenesis.

Ramboll is trying to apply its PBPK model to the lung, but IRIS identified chloroprene as a multi-site carcinogen. The NTP chloroprene mouse and rat inhalation bioassays reported significantly increased incidence of neoplasms in liver, lung, forestomach, Harderian gland, mammary gland, Zymbal's gland, kidney and the circulatory system in mice and in the lung, mammary gland, thyroid, kidney, and the oral cavity in rats (NTP, 1998). The 2010 IRIS assessment utilized multi-tumor modeling in derivation of the

inhalation unit risk (IUR). Thus, if this model is ever used to inform an IRIS assessment - and we recommend that it does not, at least not in its current flawed form (see comments of Dr. Hattis and colleagues) - that EPA apply it in a multi-tumor context.

The PBPK model has significant uncertainty. Use of the model would introduce even more uncertainty.

If EPA uses this PBPK model in any way to inform its chloroprene evaluation, EPA must still address all cancer endpoints, and the whole evaluation should go through the rigorous process of a full IRIS assessment.

Thank you for the opportunity to provide comments.

Sincerely,