March 16, 2018

Dear Members of the North Carolina Secretaries' Science Advisory Board,

We are writing in support of the drinking water health goal derived by the NC Department of Health and Human Services (NC DHHS) for the compound known as "GenX." The 140 parts per trillion health goal established by the NC DHHS was based on the use of the best available data, a point of departure (POD) relevant to human health, and on scientifically defensible and transparent choices in how the health goal was established.

We are both active researchers related to understanding the toxicity of emerging environmental contaminants. Dr. Jamie DeWitt is an Associate Professor in the Department of Pharmacology and Toxicology in the Brody School of Medicine at East Carolina University. She has been studying the toxicological effects of per- and polyfluoroalkyl substances (PFASs), the class of compounds to which GenX belongs, since 2005. She has published 13 primary research articles, five review articles, two book chapters, and edited a book on their toxicity. She has served as an external reviewer for the U.S. Environmental Protection Agency health effects assessment of perfluorooctanoic acid (PFOA) and perfluorooctane sulfonate (PFOS), the National Toxicology Program's immune effects assessment of PFOA and PFOS, and was a member of the International Agency for Research on Cancer working group for the assessment of the carcinogenicity of PFOA. Dr. Scott Belcher, a Professor in the Biological Sciences Department at North Carolina State University, is an endocrine pharmacologist and toxicologist whose research has defined mechanisms of low dose toxicity and nuclear receptor mediated signaling. He has served as a member on US EPA – FIFRA Scientific Advisory Panels, and on panels assessing chemical safety testing methods and toxicity of endocrine disrupting chemicals and emerging contaminants of concern for the Organization for Economic Co-operation and Development (OECD) and the World Health Organization/Food and Agriculture Organization of the United Nations.

We are both on the team of scientists from North Carolina State University, East Carolina University, the NC Department of Public Health, and the NC RiverKeepers to understand how long GenX stays in the human body. This study has been funded by the National Institutes of Health. We also both have been involved in risk assessments of specific compounds and sites and are highly familiar with the risk assessment process, especially with respect to the establishment of reference doses (RfDs) and derivation of health goals to protect public health.

With respect to the GenX health goal, it is apparent that the NC DHHS used the best available data. Few scientific research reports of the toxicity of GenX have been published. Of those published, one (Rae et al., 2015) would be highly suitable for establishment of a RfD as chronic toxicity and carcinogenicity of GenX was evaluated in a rat model. In this analysis, a chronic non-cancer no observed adverse effect level (NOAEL) of 0.1 mg/kg/day was identified based on an increase in the A/G (albumin to globulin) ratio (see Table 1). This endpoint is an established marker of liver health, but alone, may not be the most robust marker of an "adverse" response following exposure to a toxic agent as it may

represent a transient or "adaptive response" to liver injury. Therefore, the NOAEL for this endpoint would not be highly defensible as changes to the A/G ratio are not universally accepted as markers of an adverse response. Similarly, the previous health goal for GenX established by the NC DHHS was based on a NOAEL for a cancer endpoint (1.0 mg/kg/day based on pancreatic and testicular tumors in rats, Rae et al., 2015), which would not be the best choice for a non-cancer health goal.

Because a GenX production facility operates in The Netherlands, results of additional published toxicity studies submitted to the Dutch government (Beekman et al., 2016) were also available to the NC DHHS. Summary findings from these additional studies are listed in Table 1. The NC DHHS POD for the 140 parts per trillion health goal was also supported by four additional studies, which makes this POD a scientifically defensible choice. The POD used by the NC DHHS (0.1 mg/kg/day) was supported by the Rae et al. (2015) NOAEL, a one-generation study in mice, a 90-day study in mice, and an additional 90-day study in rats (all listed in Table 1).

The endpoint ultimately chosen as the POD by the NC DHHS was liver single cell necrosis. According to Krishna (2017), liver necrosis is an indicator of acute or ongoing injury and single cell necrosis is the death of individual liver cells. The underlying causes can be varied. We understand that this particular choice has been challenged as not being relevant to humans, based largely on an article published in 2018 (Corton et al., 2018) that addresses misconceptions about the peroxisome proliferator activated receptor alpha (PPARα)-mediated rodent liver tumor response. This article carefully articulates several key events involved in a proposed adverse outcome pathway of PPARα-mediated hepatocarcinogenesis in rodents, and whether these key events are applicable to liver tumor production in humans. One of the key events (KE3) is perturbation of cell growth and survival, which would encompass cell necrosis. However, necrosis is not considered a key PPARα-mediated event in rodent hepatocarcinogenesis. The opposite, suppression of programmed cell death (apoptosis), is a key event.

Therefore the liver endpoint chosen by the NC DHHS cannot be dismissed out of hand as being irrelevant to humans for the following reasons:

1) Liver necrosis is not a key event in PPARα-mediated rodent hepatocarcinogenesis.
2) Liver toxicity in general, across species, can be PPARα-mediated or mediated by myriad other processes and pathways.
3) No evidence exists to suggest that liver single cell necrosis is a PPARα-mediated event.

Finally, the NC DHHS should be commended on their clear and transparent articulation of the processes and procedures used for establishing their health goal.

- NC DHHS explained that the previous health goal was based on a NOAEL of 1.0 mg/kg/day.

- NC DHHS described why they updated the health goal based on a NOAEL of 0.1 mg/kg/day.

- NC DHHS stated how uncertainty factors and the relative source contribution adjustment were made.

It is most clear that the NC DHHS has followed acceptable procedures for establishing the health goal of GenX. The NC DHHS has consulted within and outside of the agency to ensure that they derived a health goal based on the best available data, chose a POD relevant to human health, made scientifically defensible choices, and were transparent in how they established the health goal.

We fully support the rationale that the NC DHHS used to establish the health goal for GenX in North Carolina, and agree that it is appropriate given current knowledge.

We understand that the health goal may change given availability of new scientific information, and trust that the NC DHHS, in cooperation with the NC Department of Environmental Quality and their partners, will do what is best for the citizens of North Carolina.

Sincerely,

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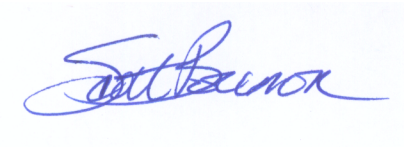

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Table 1. NOAELs from GenX studies: National Institute for Public Health and the Environment of The Netherlands (Beekman et al., 2016).

Table 6. Derived NOAELs for repeated dose toxicity.

Species	Duration	NOAEL mg/kg bw/day	LOAEL mg/kg bw/day	Effects	Reference
Rat	28 days	0.3	30	Reduction in cholesterol	Exp supporting repeated dose toxicity: oral.001
	90 days	0.1	10	A/G ratio increased Reduction in cholesterol Increased liver weight Increased kidney weight	Exp supporting repeated dose toxicity: oral.002
	Chronic	0.1	1	A/G ratio increased	Rae et al, 2015
Mouse	28 days	0.1	3	A/G ratio increased Reduced Hb Liver single cell necrosis	Exp supporting repeated dose toxicity: oral.003
	90 days	0.1	1	Increased liver weight Liver hypertrophy	Exp supporting repeated dose toxicity: oral.007
Rat	Carcinogenicity	1	50	Increase in testis and pancreatic tumours	Rae et al, 2015
	Developmental study	10	100	Early delivery Reduced fetal weights	Developmental toxicity/teratogenicity
Mouse	1-generation study	0.1	0.5	Single cell necrosis in the liver	Exp Supporting Toxicity to reproduction.002

References

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