NC Department of Health and Human Services

GenX Benchmark Dose Modeling Report

Beth Dittman, MS
Toxicologist and Health Risk Assessor
Division of Public Health, N.C. DHHS

June 18, 2018
Toxicity Studies

• Seven repeat oral dose studies provided by the registrant ≥ 28-day exposure
  – 28-day Mice
  – 28-day Rats
  – 90-day Mice
  – 90-day Rats
  – 2-year Rats
  – Reproductive Screen Mice
  – Prenatal and Developmental Rats
Endpoint Selection

• Compiled dose-response data
• Consulted with U.S. EPA team
• Based on this input, OEEB reviewed each endpoint for the following:
  – an apparent dose-response trend,
  – sensitivity and adversity of the endpoint,
  – the endpoint’s relevance to human health,
  – the magnitude of response for each endpoint, and;
  – consistency in the response for each endpoint across studies.
Endpoint Selection

• Hepatic and Hematology endpoints:
  – Consistently observed across studies
  – Observed at lower doses than other endpoints

• Developmental Endpoints:
  – Included to address concerns about sensitive and vulnerable populations

• Some endpoints demonstrated sex-specific differences – males often more sensitive

• Some endpoints were measured at different timepoints in the 2-year rat study
Modeling Parameters

• EPA’s Benchmark Dose Software (BMDS) version 2.7.0.4

• BMDS Wizard version 1.11

• Standard benchmark response (BMR)
  − Dichotomous Data = 10% extra risk
  − Continuous Data = one standard deviation change from the control mean

• Benchmark Dose Lower Bound (BMDL) = lower end of a one-sided 95% confidence limit on the benchmark dose

• BMDS Wizard used to create output reports and BMD-to-BMDL ratio was added to these reports
Benchmark Dose Modeling Results

• Hematological Effects
  − BMDLs range from 0.00589 to 25.3 mg/kg/day
  − Lowest hematological BMDL without a warning flag is 0.357 mg/kg/day – decreased hematocrit in male rats from the 28-day rat study

• Hepatic Effects
  − BMDLs range from 0.0741 to 5.55 mg/kg/day
  − Lowest hepatic BMDL without a warning flag is 0.151 mg/kg/day – single cell hepatocellular necrosis in male mice from the reproductive screen

• Developmental Effects
  − BMDLs range from 3.06 to 635 mg/kg/day
  − Lowest developmental BMDL without a warning flag is 3.06 mg/kg/day – decreased offspring weight at postnatal day 21 in male mice from the reproductive screen
Limitations

• Purpose was to respond to SAB request to better refine the point of departure

• Not intended as a comprehensive review of all scientific information

• Not all endpoints were modeled for this report
  – Focus on endpoints seen at lowest doses and observed consistently across studies and developmental effects

• Does not discuss other factors used to calculate the provisional health goal
Conclusions and Next Steps

• Completed benchmark dose modeling for selected endpoints from GenX toxicity studies

• N.C. DHHS asks that the SAB consider this information when making recommendations regarding health or regulatory levels for GenX in the state of North Carolina
Questions?