NC Department of Health and Human Services

GenX Benchmark Dose Modeling Report

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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?