**Code\_Explanation**

The code consists of four parts: rat.code, mice.code, human.code, and figure.code。part1：Model development, simulation, and evaluation of the PBPK model for rats；part2：Evaluation and exposure dose estimation of the PBPK model for mice；part3：Evaluation, dose calculation, and health risk assessment of the PBPK model for humans；part4：All codes used to generate the figures in the manuscript and the Supplemental Material file.

1. **Rat.code**

In this part, all codes are divided into three sections: model development (Lines 1-205), simulation (Lines 216-450), and evaluation of the PBPK model for rats (Lines 216-450).

**1.1Model development (Lines 1-205)**

Lines 1–22: load the required R packages.

Lines 23–133: load the Rat-Gd-IV-PBPK model.

Lines 134–205: load the event settings for intravenous injection.

**1.2 Model simulation (Lines 206-470)**

Lines 206–308: identify and modify the sensitive parameters. Run the code in lines 206–261 to generate the "Sen" plot, which displays the results of the sensitivity analysis. Then, in lines 265–307, adjust the sensitive parameters identified in the previous step using the Nelder-Mead method, setting the fluctuation range to 20-fold until the optimal simulated parameters are obtained.

Lines 309–470: perform sensitivity analysis. Run the code in lines 311–403 to obtain the initial concentrations of target organs. Then, run the code in lines 404–470 to change each parameter by 1% and calculate the corresponding changes in organ concentrations. Save the results as "Rat-sensitive analysis-data" for generating Figure 6C.

**1.3 Model evaluation (Lines 473-711)**

Lines 473–563: load the rat-oral-PBPK model.

Lines 563–711: load the event settings for oral exposure. In lines 602–607, set the absorption rate for oral exposure and the fecal absorption rate, which sum up to 1. In lines 612–636, specify that the absorbed HREE directly enters the liver blood, while the unabsorbed portion is excreted directly into bile. Save the results as "Rat-validation-oral-predicted-data.csv", and then use the code in figure.code along with the actual.data to generate evaluation plots.

1. **Mice.code**

In this part, all codes are divided into three sections: model development (Lines 1–258), evaluation of the PBPK model for mice (Lines 258–381), and external exposure calculation (Lines 386–519).

**2.1 Model development (Lines 1-258)**

Lines 1–22: load the required R packages.

Lines 23-56: convert rat parameters to mice parameters.

Lines 57-257: load the mouse PBPK model. Replace the output of print(rat) back into the original PBPK model and update the remaining physiological parameters accordingly.

**2.2 Model evaluation (Lines 258-381)**

Lines 258-381: load the event settings for oral exposure. The design of absorption rate and absorption compartment follows the same approach as described in Section 4.1.3. Save the results as "mice-28-oral-predicted-data.csv", and then use the code in figure.code along with the actual.data to generate evaluation plots.

**2.3 External exposure calculation(Lines 386-519)**

Lines 258–381: calculate external exposure based on internal exposure. In lines 386–486, set up the PBPK model for mice. In lines 487–519, set the target organ to the liver, then define a dose range to find the external exposure dose that results in the liver concentration closest to the target value.

1. **Human.code**

In this part, all codes are divided into three sections: model development (Lines 1–140), evaluation of the PBPK model for human (Lines 140-303), and Health Risk assessment (Lines 304-911).

**3.1 Model development (Lines 1-140)**

Lines 1–25: load the required R packages.

Lines 26-60: convert rat parameters to mice parameters.

Lines 61-140: load the mouse PBPK model. Replace the output of print(human) back into the original PBPK model and update the remaining physiological parameters accordingly.

**3.2 Model evaluation (Lines 140-303)**

Lines 140-303: load the event settings for oral exposure. The design of absorption rate and absorption compartment follows the same approach as described in Section 4.1.3. Save the results as "human-50years-oral-predicted-data.csv", and then use the code in figure.code along with the actual.data to generate evaluation plots.

**3.3 Health risk assessment (Lines 304-911)**

Lines 304-911: Calculate the Uncertain Factor. In lines 305–543, calculate the organ concentrations of HREE after 50 years of continuous oral exposure at 1 mg/kg/day using the PBPK model for humans. In lines 544–868, calculate the organ concentrations of HREE after 28 days of continuous oral exposure at 1 mg/kg/day using the PBPK model for mice. In lines 869–911, calculate the time-concentration AUC for human and mice organs, and determine the Uncertainty Factor based on their ratios.