Hepatic Impairment Test Cases

**Healthy Individual:**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Species | Population | Gender | Age (years) | Weight (kg) | Height (cm) | BMI (kg/m2) |
| Human | European | Male | 30 | 73 | 176 | 23.57 |

**Portal Blood Flow (Qrest)**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Organ** | **Units** | **Healthy Individual** | **Child-Pugh A (0.4)** | **Child-Pugh B (0.36)** | **Child-Pugh C (0.04)** | **Reference** |
| **Stomach** | mL/min/100g organ | 38.61 | 15.444 | 13.8996 | 1.5444 | [1] |
| **Small Intestine** | mL/min/100g organ | 89.77 | 35.908 | 32.3172 | 3.5908 | [1] |
| **Large Intestine** | mL/min/100g organ | 63.05 | 25.22 | 22.698 | 2.522 | [1] |
| **Spleen** | mL/min/100g organ | 80.11 | 32.044 | 28.8396 | 3.2044 | [1] |
| **Pancreas** | mL/min/100g organ | 34.16 | 13.664 | 12.2976 | 1.3664 | [1] |

\*Each scaling factor of healthy individual is located in brackets across Child-Pugh Scores

**Hepatic Arterial Blood Flow**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Organ** | **Units** | **Healthy Individual** | **Child-Pugh A (1.3)** | **Child-Pugh B (2.3)** | **Child-Pugh C (3.4)** | **Reference** |
| **Hepatic Arterial Blood Flowa** | mL/min/100g organ | 17.94 | 23.322 | 41.262 | 60.996 | [1] |

aDesignated as liver blood flow in PK-Sim

\*Each scaling factor of healthy individual is located in brackets across Child-Pugh Scores

Units: mL/min/100g organ

**Liver Volume**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Organ** | **Units** | **Healthy Individual** | **Child-Pugh A (0.69)** | **Child-Pugh B (0.55)** | **Child-Pugh C (0.28)** | **Reference** |
| **Liver Volume** | Litres | 2.38 | 1.6422 | 1.309 | 0.6664 | [1] |

\*Each scaling factor of healthy individual is located in brackets across Child-Pugh Scores

**Renal Blood Flow**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Organ** | **Units** | **Healthy Individual** | **Child-Pugh A (0.88)** | **Child-Pugh B (0.65)** | **Child-Pugh C (0.65)** | **Reference** |
| **Renal Blood Flowa** | mL/min/100g organ | 302.705 | 266.3804 | 196.75825 | 196.75825 | [1] |

aDesignated as kidney blood flow in PK-Sim

\*Each scaling factor of healthy individual is located in brackets across Child-Pugh Scores

**Glomerular Filtration Rate (GFR)**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Parameter** | **Healthy Individual** | **Child-Pugh A (1)** | **Child-Pugh B (0.7)** | **Child-Pugh C (0.36)** | **Reference** |
| **GFR Fraction** | 1 | 1 | 0.7 | 0.36 | [1] |

\*In this scenario GFR fraction within the molecule building blocks were adjusted across the Child-Pugh Scores. IF not possible within the algorithm can adjust GFR within the individual

**Other Organs (Qother)**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Organ** | **Units** | **Healthy Individual** | **Child-Pugh Aa** | **Child-Pugh Bb** | **Child-Pugh Cc** | **Reference** |
| **Bone** | mL/min/100g organ | 2.75 | 3.59 | 5.071717768 | 6.229599311 | [1] |
| **Fat** | mL/min/100g organ | 2.18 | 2.84 | 4.020488994 | 4.938373272 | [1] |
| **Gonads** | mL/min/100g organ | 8.06 | 10.53 | 14.86474371 | 18.25838925 | [1] |
| **Heart** | mL/min/100g organ | 62.34 | 81.45 | 114.9712311 | 141.2193531 | [1] |
| **Muscle** | mL/min/100g organ | 3.42 | 4.46 | 6.307372642 | 7.747356234 | [1] |
| **Skin** | mL/min/100g organ | 8.65 | 11.30 | 15.95285771 | 19.59492147 | [1] |

aScaling factor for Child-Pugh A determined to be 1.30661110697457

bScaling factor for Child-Pugh B determined to be 1.844261006

cScaling Factor for Child-Pugh C determined to be 2.26530884

**How to Calculate:**

Disease Factorcardiac index = (Qother x Disease Factorother + Qrest x Disease Factorrest + Qbrain)/ (Qother + Qrest + Qbrain)

Qrest (L/min) = sum of all healthy values of portal, hepatic arterial and renal blood flow

Qother (L/min) = sum of all healthy values of “other organs”

Qbrain (L/min) = blood flow to brain of healthy individual

Qrest x Disease factorrest = Sum of Child-Pugh adjusted values for Qrest

Disease Factorcardiac index = Child-Pugh A: 1.11, Child-Pugh B: 1.27, Child-Pugh C: 1.36

**Solve for Disease Factorother**

\*\*Disease FactorOther to be used as scaling factor shown in table above

Please see: <https://github.com/Open-Systems-Pharmacology/Forum/discussions/1341> for further explanation if needed

**Hepatic Intrinsic Clearance**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Enzyme** | **Healthy Individual (µmol/L)** | **Child-Pugh A (SF)** | **Child-Pugh B (SF)** | **Child-Pugh C (SF)** | **Reference** |
| **CYP3A4** | 4.32 | 4.32 (1) | 1.728 (0.4) | 1.728 (0.4) | [1] |
| **CYP1A2** | 1.80 | 1.80 (1) | 0.18 (0.1) | 0.18 (0.1) | [1] |
| **CYP2E1** | 1.96 | 1.96 (1) | 1.63 (0.83) | 1.63 (0.83) | [1] |
| **CYP2A6** | 2.72 | 2.42 (0.89) | 1.69 (0.62) | 0.87 (0.32) | [2] |
| **CYP2B6** | 1.56 | 1.56 (1) | 1.404 (0.9) | 1.25 (0.8) | [2] |
| **CYP2C8** | 2.56 | 1.77 (0.69) | 1.33 (0.52) | 0.82 (0.32) | [2] |
| **CYP2C9** | 3.84 | 2.65 (0.69) | 1.96 (0.51) | 1.27 (0.33) | [2] |
| **CYP2C18** | 0.10 | 0.064 (0.32) | 0.026 (0.26) | 0.012 (0.12) | [2] |
| **CYP2C19** | 0.76 | 0.24 (0.32) | 0.198 (0.26) | 0.0912 (0.12) | [2] |
| **CYP2D6** | 0.40 | 0.304 (0.76) | 0.132 (0.33) | 0.044 (0.11) | [2] |

SF; scaling factor applied to each enzymes reference concentration

**Fraction Unbound:**

Must be adjusted in molecule building blocks

Eq: Fu =

fprotein: Volume fraction of plasma binding proteins (2.2% for albumin; 0.04% AAG)

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Volume of Protein (fprotein) | Healthy Individual | Child-Pugh A Scaling Factor | Child-Pugh B  Scaling Factor | Child-Pugh C  Scaling Factor | Reference |
| Albumin  AAG | 0.022  0.0004 | 0.81  0.6 | 0.68  0.56 | 0.5  0.3 | [1] |

Kprotein: rearrange equation to calculate using fraction unbound in healthy adults

Fu: fraction unbound

**Hematocrit:**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Parameter | Healthy Individual | Child-Pugh A (0.92) | Child-Pugh B (0.88) | Child-Pugh C (0.83) | Reference |
| Hematocrit | 0.43a | 0.39 | 0.37 | 0.35 | [1] |

\*Scaling factor located in brackets

aUsed value of 0.43 for healthy individual, will be sex differences between individuals however scaling factors are maintained.

**References:**

[1] Edginton AN, Willmann S. Physiology-based simulations of a pathological condition: prediction of pharmacokinetics in patients with liver cirrhosis. Clin Pharmacokinet. 2008;47(11):743-52.

[2] Johnson TN, Boussery K, Rowland-Yeo K, Tucker GT, Rostami-Hodjegan A. A semi-mechanistic model to predict the effects of liver cirrhosis on drug clearance. Clin Pharmacokinet. 2010;49(3):189-206.