**Pharmacokinetics-Based Pediatric Dose Evaluation and Optimization using Saliva – a Case Study**

**Supplementary Files**

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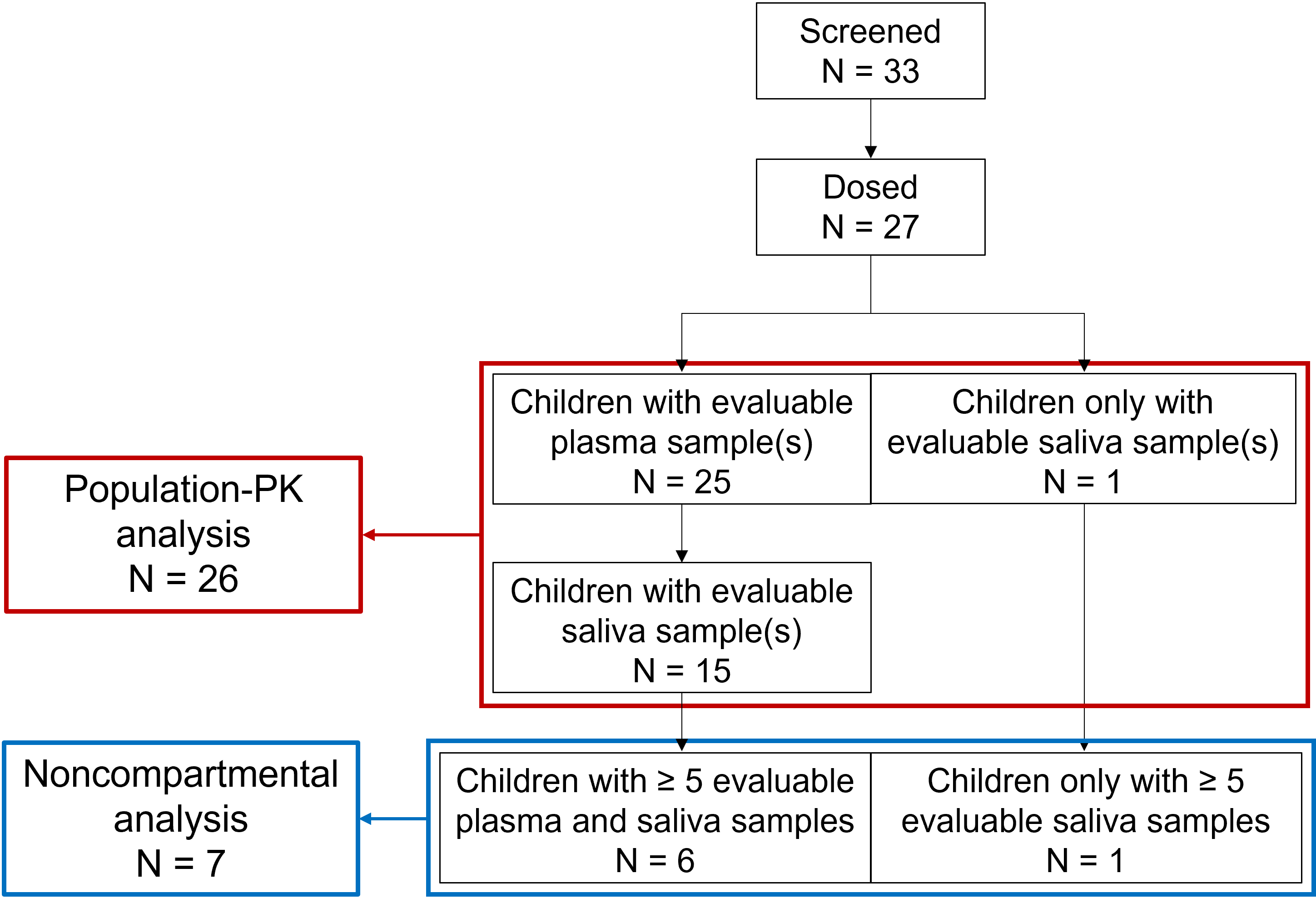
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*Supplementary Table S1: Pharmacokinetic (PK) parameters of metamizole metabolites in saliva and plasma after a single intravenous dose of 10 mg/kg in children from which at least 5 evaluable saliva samples were collected*

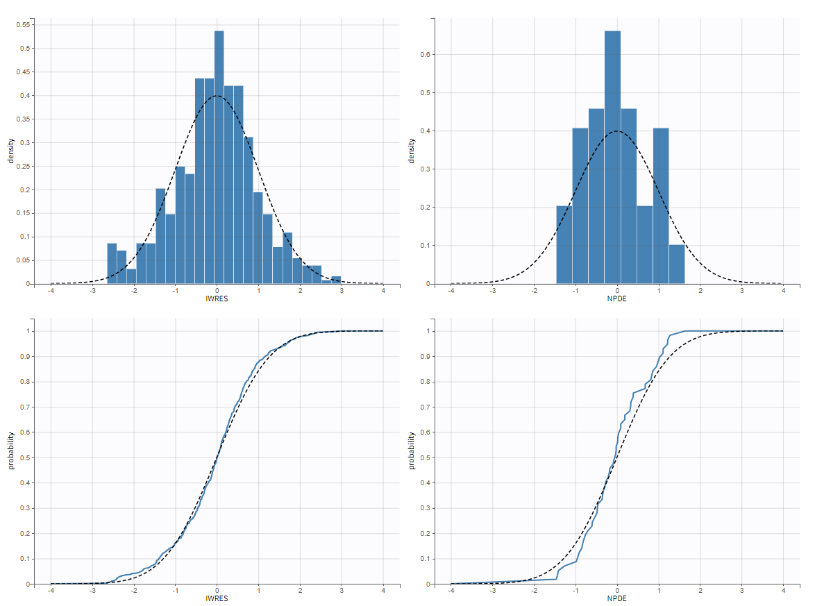
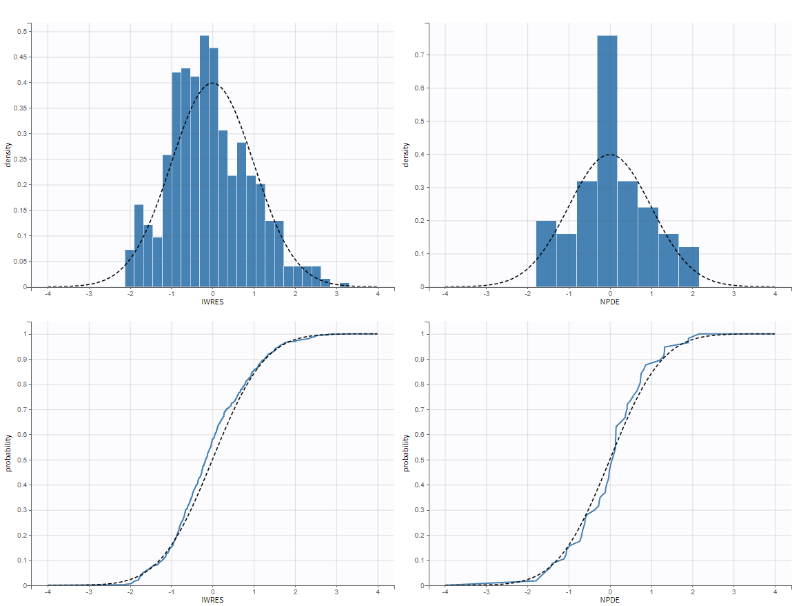
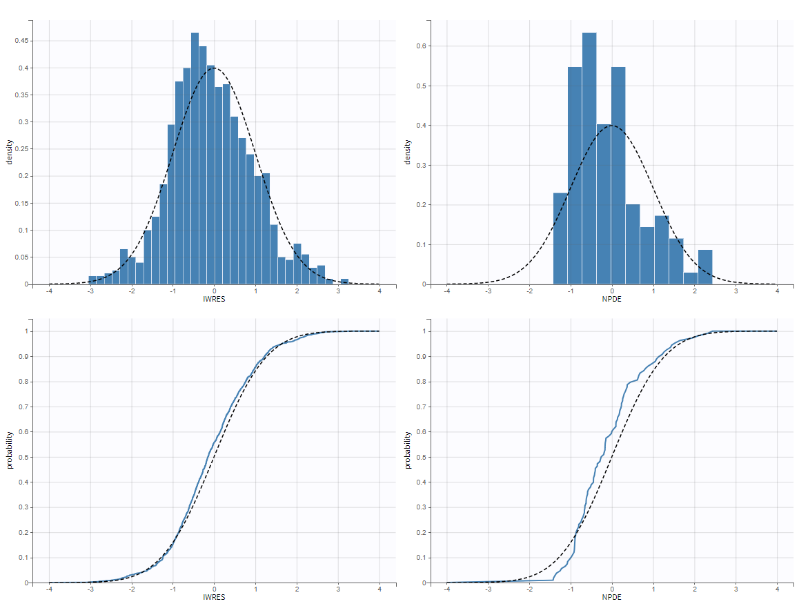
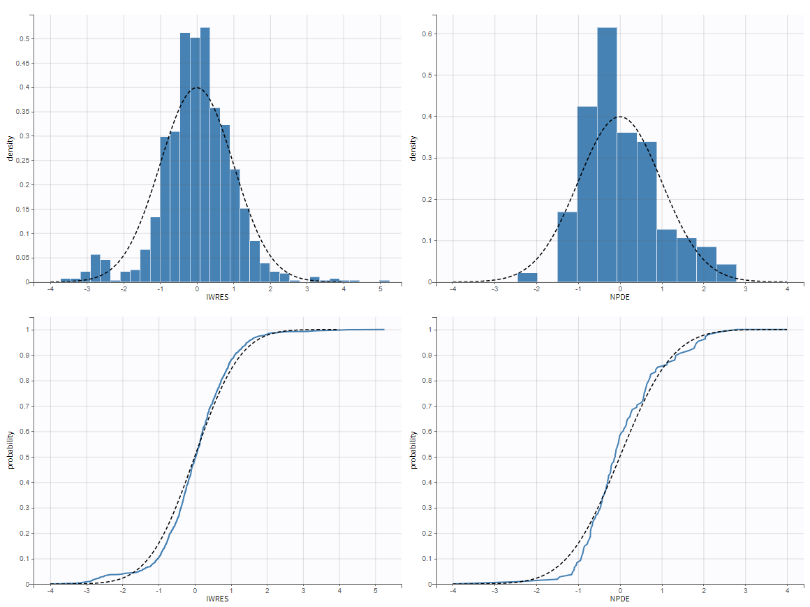
|  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  |  |  | 4-MAA | | 4-AA | | 4-FAA | | 4-AAA | | |
| Parameter [unit] | Statistic |  | Saliva  (N = 7) | Plasma  (N = 6) | Saliva  (N = 7) | Plasma  (N = 6) | Saliva  (N = 7) | Plasma  (N = 6) | Saliva  (N = 7) | Plasma  (N = 6) | |
| **Cmax [ng/mL]** | **Geometric mean** |  | **2741** | **8055** | **398** | **683** | **1891** | **1340** | **1179** | **1087** | |
|  | 95% CI of geometric mean |  | 1414, 5315 | 6340, 10232 | 269, 590 | 435, 1072 | 1384, 2583 | 951, 1890 | 597, 2329 | 600, 1966 | |
| **tmax [h]** | **Median** |  | **1.0** | **1.0** | **2.0** | **2.0** | **4.1** | **4.9** | **5.8** | **5.9** | |
|  | Range |  | 1.0, 2.3 | 1.0, 1.2 | 1.0, 9.0 | 1.1, 6.0 | 1.0, 6.1 | 4.0, 6.0 | 2.0, 9.0 | 4.0, 9.0 | |
| **AUC0–t [ng·h/mL]** | **Geometric mean** |  | **8252** | **26406** | **2781** | **4266** | **15412** | **11535** | **10375** | **8853** | |
|  | 95% CI of geometric mean |  | 4594, 14823 | 20225, 34475 | 1514, 5108 | 2121, 8578 | 9528, 24931 | 7536, 17655 | 5227, 20594 | 5291, 14814 | |
| **AUC0–∞ [ng·h/mL]a** | **Geometric mean** |  | **8571** | **27962** | **-** | **-** | **-** | **-** | **-** | **-** | |
|  | 95% CI of geometric mean |  | 4746, 15480 | 20076, 38946 | **-** | **-** | **-** | **-** | **-** | **-** | |
| **t½ [h]1** | **Geometric mean** |  | **3.3** | **2.3** | **-** | **-** | **-** | **-** | **-** | **-** | |
|  | 95% CI of geometric mean |  | 1.9, 5.6 | 1.7, 3.2 | **-** | **-** | **-** | **-** | **-** | **-** | |
| Actual sampling times were used and all concentrations below lower limit of quantification were imputed with zero. Cmax and tmax were derived from the individual measured concentrations. AUC0–t was calculated with the linear trapezoidal rule. AUC0–∞ and t½ were determined based on the terminal elimination rate constant derived by log-linear regression analysis. PK parameters were summarized by geometric mean and 95% CI (except for median and range for tmax).  a For 4-AA, 4-FAA, and 4-AAA, no t½ and, consequently, no AUC0–∞ were determined based on too few data points during the terminal elimination phase.  4-AA = 4-aminoantipyrine, 4-AAA = 4-acetyl-aminoantipyrine, 4-FAA = 4-formyl-aminoantipyrine, 4-MAA = 4‑methylaminoantipyrine, AUC0–t = Area under the saliva concentration-time curve from zero to the last measurement above the limit of quantification, AUC0–∞ = Area under the saliva concentration-time curve from zero to infinity, Cmax = Maximum plasma concentration, t½ = Terminal half-life, tmax = Time to reach maximum plasma concentration. CI = Confidence interval.  Out of 27 children who were enrolled, 16 provided saliva samples. For a direct comparison, the plasma PK were calculated for the same subset of children providing saliva samples, except for 1 child, from whom only saliva samples were available. | | | | | | | | | | |

*Supplementary Table S2: Number of available plasma and saliva samples per sampling time point*

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  |  | Sampling time points (h) | | | | | | |
| Matrix | Metabolite | 1 | 2 | 4 | 6 | 8 | 10 | 24 |
| Saliva | 4-MAA | 13 | 9 | 13 | 12 | - | 9 | 4 |
| 4-AA | 13 | 9 | 13 | 12 | - | 9 | 4 |
| 4-FAA | 13 | 9 | 13 | 12 | - | 9 | 4 |
| 4-AAA | 13 | 9 | 13 | 12 | - | 9 | 4 |
| Plasma | 4-MAA | 26 | 22 | 21 | 20 | 1 | 19 | 6 |
| 4-AA | 26 | 22 | 21 | 20 | 1 | 19 | 6 |
| 4-FAA | 26 | 22 | 21 | 20 | 1 | 19 | 6 |
| 4-AAA | 26 | 22 | 21 | 20 | 1 | 19 | 6 |

*Supplementary Figure S1: Flow chart of enrolled and dosed children and number of children providing plasma and/or saliva samples*

*Supplementary Figure S2: Correlations between individual distribution fraction parameters saliva to plasma (FS/P) for 4-MAA with [A] the children’s age and [B] albumin concentrations as well as FS/P for 4-AA and [C] the children’s age and [D] albumin concentrations. Solid line = linear regression, grey-shaded area = 95% confidence interval*

***Supplementary Figure S3: Normalized Prediction Distribution Errors and individual weighted residuals plots for the final population PK model of 4-MAA and 4-AA in plasma and saliva*

**4-AA saliva**

**4-MAA saliva**

**4-MAA plasma**

**4-AA plasma**

*Supplementary Figure S4: [A] Visual predictive checks (points = observed concentration data over time, lines = median, 5th, and 95th percentile of observed data, shaded area = 90% prediction interval of median and 10th and 90th percentile of the simulations, linear scales) and [B] observation versus prediction plots for the final population PK model of 4-MAA and 4-AA in plasma and saliva (points = concentration, solid line = line of identity, logarithmic scales)*

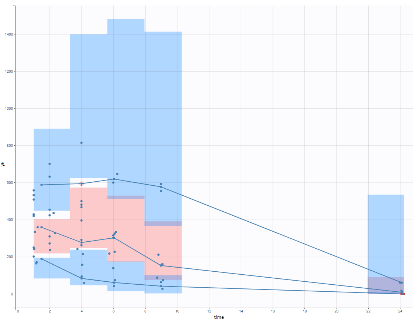
**4-MAA plasma**

**4-MAA saliva**

**4-AA saliva**

**4-AA plasma**

**[A]**

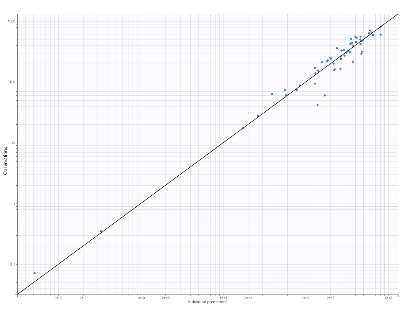
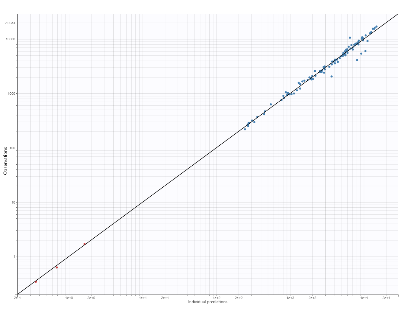
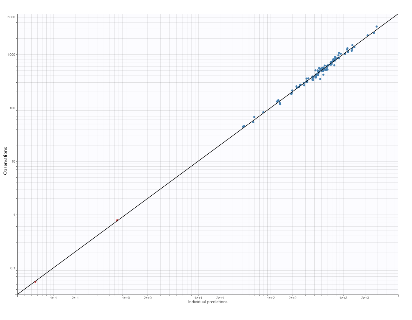
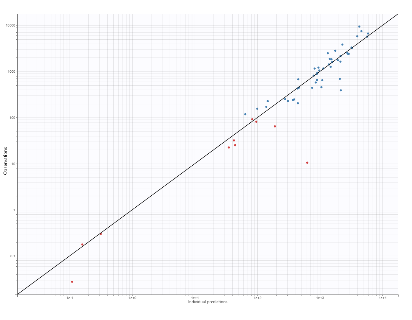
Chart

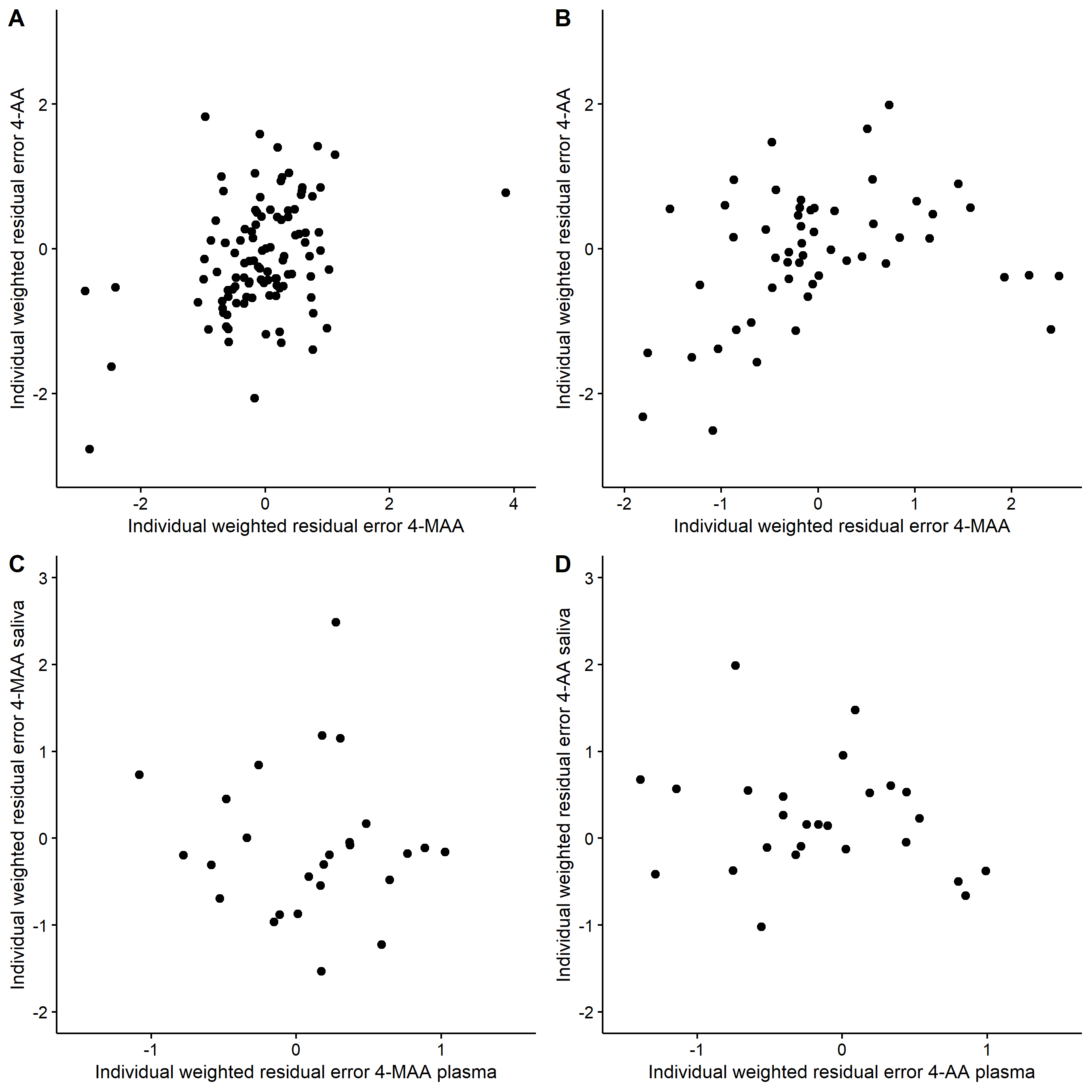
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**[B]**



*Supplementary Figure S5: Correlation between residual errors of 4-AA versus 4-MAA in [A] plasma and [B] saliva as well as residual errors of saliva versus plasma of [C] 4-MAA and [D] 4-AA. Suggested correlation was not considered in the model as it did not improve the fit*