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1 **Dose evaluation of intravenous metamizole (dipyrone) in infants and children: a**  
2 **prospective population pharmacokinetic study**

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54

55 **ABSTRACT**

56 Purpose: The prodrug metamizole is prescribed intravenously for postoperative pain in children,  
57 including off-label use in infants <1 year. We aimed to assess the pharmacokinetics of the main  
58 metabolites of metamizole in children aged 3-72 months.

59 Methods: A single dose of 10 mg/kg metamizole was administered intravenously for  
60 postoperative analgesia. Pharmacokinetic samples were drawn at predefined time points.  
61 Pharmacokinetics of the main active metabolite 4-methylaminoantipyrine and three other  
62 metabolites was characterized by both non-compartmental and population pharmacokinetic  
63 analysis.  $AUC_{0-inf}$  of 4-methylaminoantipyrine was calculated by non-compartmental analysis for  
64 two age cohorts (3-23 months, 2-6 years) and compared to the 80-125% range of adult dose-  
65 adjusted reference exposure ( $AUC_{ref}$ ). Population pharmacokinetic analysis investigated age and  
66 weight dependency of the pharmacokinetics, and optimal dosing strategies to achieve equivalent  
67 adult exposure.

68 Results: A total of 25 children aged 5 months - 5.8 years (7.8-24.8 kg) with at least one  
69 concentration sample were included, 19 children had  $\geq 5$  predefined samples up to 10h after  
70 metamizole dose administration.  $AUC_{0-inf}$  of 4-methylaminoantipyrine in children 2-6 years was  
71 29.8 mg/L\*h (95%CI 23.3-38.1), significantly lower than  $AUC_{ref}$  (80%-125% range: 39.2-61.2  
72 mg/L\*h).  $AUC_{0-inf}$  of 4-methylaminoantipyrine in infants < 2 years was 42.5 mg/L\*h (95%CI 15.7-  
73 115.4), comparable to  $AUC_{ref}$ , while infants <12 months showed increased exposure. Observed  
74 variability could be partially explained by covariates weight and age.

75 Conclusions: Age-related changes in pharmacokinetics of 4-methylaminoantipyrine requires  
76 reduced weight-based IV dosing in infants <1 year compared to infants and children up to 6 years  
77 (5 versus 10-20 mg/kg) to achieve equivalent adult exposure.

78 (ClinicalTrials.gov Identifier: NCT02660177)

79  
80 Key words: Metamizole, dipyrrone, pharmacokinetics, children, infants

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83 **Abbreviations:**

1			
2	84	AA	4-aminoantipyrine
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4	85	AAA	4-acetylaminoantipyrine
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7	86	ADR	adverse drug reaction
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10	87	AE	Adverse events
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12	88	AIC	Akaike information criterion
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14	89	AUC	area under the curve
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16			
17	90	BSV	between-subject variability
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19	91	CL	clearance
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22	92	C <sub>max</sub>	maximal plasma concentration
23			
24	93	COX	cyclooxygenase
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26	94	CYP	cytochrome P450
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28			
29	95	FAA	4-formylaminoantipyrine
30			
31	96	IV	intravenously, intravenous
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33			
34	97	k <sub>h</sub> ,	hydrolysis rate of metamizole, MAA formation rate
35			
36	98	LLOQ	lower limit of quantification
37			
38	99	MAA	4-methylaminoantipyrine
39			
40			
41	100	NAT2	N-acetyltransferase 2
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43			
44	101	OFV	objective function value
45			
46	102	PACU	post-anesthesia care unit
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49	103	PK	pharmacokinetics(s)
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51	104	PPK	Population PK
52			
53	105	t <sub>1/2</sub>	elimination half-life
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55			
56	106	T <sub>max</sub>	time of C <sub>max</sub>
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58	107	TV	typical value
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108 VPC visual predictive check

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## 111 1 INTRODUCTION

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3 112 Metamizole, or dipyrone, is a pyrazolone derivative used for treatment of severe pain and/or fever  
4 113 [1]. It has spasmolytic properties and a favorable safety profile regarding gastrointestinal, hepatic  
5  
6 114 and renal adverse effects compared to other non-opioid analgesics [2, 3]. Its use is, however,  
7  
8 115 questioned due to a rare risk of potentially life-threatening agranulocytosis, the reason why it has  
9  
10 116 been banned in multiple countries [4]. The exact mechanism of analgesic action is not fully  
11 117 understood. Inhibition of cyclooxygenase isoforms 1 and 2 and of prostaglandin E<sub>1</sub> and E<sub>2</sub>  
12 118 synthesis has been demonstrated. Additionally, action on opioid and cannabinoid systems as well  
13  
14 119 as activation of ATP-sensitive K<sup>+</sup> channels are well documented [5-7] .

16  
17 120 Metamizole is a prodrug that is rapidly non-enzymatically hydrolyzed to an active metabolite, 4-  
18  
19 121 methylaminoantipyrine [8]. MAA is further metabolized to another active metabolite, 4-  
20  
21 122 aminoantipyrine, and an inactive end-metabolite, 4-formyl-aminoantipyrine (Figure 1). The  
22 123 influence of cytochrome P450 enzymes on the oxidative biotransformation of MAA to AA is not  
23  
24 124 yet fully explained [9, 10]. *In vitro* and *in vivo* evidence has suggested a role for CYP2C19, and more  
25  
26 125 recently, also of other CYPs isoforms and human myeloperoxidase in granulocytes [10, 11]. AA is  
27  
28 126 acetylated to inactive 4-acetyl-aminoantipyrine by N-acetyltransferase 2 [12]. Also, AA is  
29  
30 127 assumed to be metabolized to the inactive end-metabolite FAA. In total, more than 20 metabolites  
31 128 are currently known [8].

32  
33 129 The analgesic effect of metamizole seems to correlate mainly with MAA exposure [13]. The drug  
34  
35 130 has been shown to be an effective analgesic in children at doses of 15 mg/kg [14, 15]. Metamizole  
36  
37 131 is one of the few non-opioid analgesics, along with paracetamol and ketorolac, that can be  
38  
39 132 administered intravenously, which is a significant advantage in children postoperatively. But  
40  
41 133 according to the current label, IV use is off-label in infants <12 months or with a body weight <9  
42  
43 134 kg, and intramuscular administration is recommended in these patients [16]. In practice however,  
44  
45 135 IV is favored over IM administration also in infants <12 months, since IV application allows for  
46  
47 136 complete and rapid absorption, associated with a quick onset of action, whereas IM applications  
48  
49 137 leads to erratic and delayed absorption, pain and risks of infection/inflammation at the injection  
50  
51 138 site. The licensed parenteral pediatric dosing scheme is summarized in Table 1. However, dosing  
52  
53 139 in mg/kg is more common with inconsistent dosing practices. Among Swiss pediatric hospitals for  
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55 140 example, doses ranging from 5-20 mg/kg for repetitive dosing, or even up to 40 mg/kg for a single  
56  
57 141 IV dose are used, including off-label IV use in infants of age 3-12 months [16].

58 142 Pharmacokinetics of metamizole metabolites is well described in adults (licensed dose: 500-1000  
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60 143 mg, max. 4 times daily), while such information is lacking for infants and children, despite its use  
61  
62 144 for almost 100 years. A pharmacokinetic study in children aged 1-11 years reports increased

145 urinary metabolite excretion in younger children compared to adults following a single oral dose  
146 of 8 mg/kg suggesting different pharmacokinetic properties [17]. No data in infants <1 year have  
147 been available.

148 The objective of this study was (I) to characterize the pharmacokinetics of the main metabolites  
149 of metamizole following a single IV dose for post-operative analgesia in infants and children 3 to  
150 72 months of age (two age cohorts; infants 3-23 months and children 2-6 years), (II) to propose a  
151 rationale for an optimal mg/kg-dosing strategy in infants and children.

## 152 **2 METHODS**

### 153 **2.1 Trial design**

154 A single center, open-label, prospective study was conducted at the University of Basel Children's  
155 Hospital after approval by the local ethics committee (ClinicalTrials.gov Identifier:  
156 NCT02660177) between 01/2016 and 12/2017. Infants and children aged between 3 months and  
157 6 years (72 months) of age with a body weight >5 kg, who were scheduled for elective in- or  
158 outpatient surgery with intended administration of IV metamizole as part of the local standard  
159 postoperative pain management, were eligible for the study.

160 Main exclusion criteria were premature birth, kidney or liver disease, hematological  
161 abnormalities, asthma, immunosuppression, treatment with strong CYP2C19 inhibitors or  
162 inducers or drugs known to induce agranulocytosis within 3 months prior to study, documented  
163 previous adverse drug reaction to metamizole, or treatment with metamizole within 30 days  
164 prior to study.

### 165 **2.2 Intervention**

166 After having obtained informed consent from parents of eligible patients, anthropometric  
167 parameters and medical history including concomitant treatments were recorded, and a physical  
168 examination was performed.

169 Following inhaled anesthesia, a first peripheral IV line was placed for the purpose of planned  
170 surgery and 0.7 mL of blood was drawn for biochemical and hematologic evaluation of exclusion  
171 criteria (differential blood count, urea, creatinine, ASAT, ALAT, bilirubin and albumin). A second  
172 peripheral IV line for repeated painless blood sampling was inserted at an extremity on the  
173 opposite side.

174 Before awakening from anesthesia, or immediately after arrival in the post-anesthesia care unit,  
175 patients received a single metamizole dose of 10 mg/kg (based on current body weight) through

176 the first peripheral IV line (Novalgine® 50%, metamizole injection, 500mg/mL, Sanofi-Aventis SA,  
177 Vernier, Switzerland) as intravenous injection, followed by a saline flush. Further standard  
178 postoperative pain management consisted of regular administration of paracetamol  
179 (acetaminophen) and a non-steroidal anti-inflammatory agent (ibuprofen, mefenamic acid or  
180 ketolorac), and opioids (nalbuphine, morphine) when required.

181 Blood samples, 0.5 ml each, were collected for pharmacokinetic analysis into EDTA tubes  
182 (Microvette 500 K3E, Sarstedt, Nümbrecht, Germany) at 5 predefined time points after dosing (1h,  
183 2h, 4h, 6h, 10±1h). An additional sample at 24h was collected from inpatients; patients who  
184 underwent day-surgery were discharged home after the 10±1h sample.

185 At 6 hours, i.e. at the end of a regular dosing interval, an additional 0.7 mL blood sample was drawn  
186 for biochemical and hematologic safety assessment.

### 2.3 Pharmacokinetic analyses and dose evaluation

188 Concentrations of MAA, AA, FAA and AAA were analyzed using an LC-MS/MS method according  
189 to Bachmann et al., for details see supplement S2 [9]. The calibration range was 0.025-25 mg/L  
190 for MAA, AA and AAA, and 0.025-10 mg/L for FAA, i.e. a lower limit of quantification of 0.025  
191 mg/L for all metabolites. Imprecision was max. 12.5%, inaccuracy ±15% (±20% at LLOQ).

192 Data were analysed both by non-compartmental analysis and population pharmacokinetic  
193 modelling. NCA included all patients having completed at least the predefined 5 blood samples  
194 (per protocol analysis), PPK all patients with at least one concentration sample (intention-to-treat  
195 analysis). NCA investigated exposure in two age cohorts: infants 3-23 months and children 2-6  
196 years. Detailed information on performed analyses is provided in sections 2.3.3 and 2.3.4.

#### 2.3.1 Reference exposure

198 Reference area under the plasma concentration-time curve from zero to infinity ( $AUC_{0-\infty}$ ) was  
199 derived from 3 healthy volunteer studies in adults after a dose of 1000 mg metamizole IV  
200 ( $AUC_{1000}$ ) [8, 18, 19]. The mixed effect estimate of adult MAA  $AUC_{1000}$  was re-scaled to a dose of 10  
201 mg/kg, assuming a mean patient weight of 70 kg (reference  $AUC_{ref} = AUC_{1000} \cdot (10 \text{ mg/kg}) / (1000$   
202  $\text{mg} / 70 \text{ kg}) = AUC_{1000} \cdot 0.7$ ). Median exposure range in adults after an IV dose of 500-1000 mg  
203 ( $AUC_{500}$ - $AUC_{1000}$ ) was calculated ( $AUC_{500} = AUC_{1000} \cdot 0.5$ ).

#### 2.3.2 Sample Size

205 The sample size was determined according to calculations proposed by Wang *et al.*, i.e. the study  
206 was prospectively powered to target a 95% confidence interval (95% CI) of  $AUC_{0-\infty}$ , as derived by  
207 NCA, within 80% and 125% of  $AUC_{ref}$ , with at least 80% power. Accordingly, the choice of study



208 population consisted of 13 patients per age cohort (initially 3 age cohorts were defined: cohort 1:  
209 age 3-11 months, cohort 2: age 12-23 months, cohort 3: 24-72 months, but cohorts 1 and 2 needed  
210 to be combined as explained below) [20].

### 211 2.3.3 Non-compartmental analysis

212 NCA was conducted using the *PKNCA* package in R (Version 3.2.4, R Core Team, Vienna, Austria)  
213 [21, 22]. MAA  $AUC_{0-inf}$  was calculated as primary outcome according to the linear trapezoidal rule  
214 using log-transformed measured concentrations. The 95% confidence interval (95% CI) of the  
215 geometric mean  $AUC_{0-inf}$  of MAA was compared to the 80-125% interval of adult  $AUC_{ref}$  (see  
216 above). Further parameters derived for MAA and the other metabolites were the AUC within a  
217 dosing interval of 8h ( $AUC_{0-8h}$ ), maximal plasma concentration, time of  $C_{max}$  and the elimination  
218 half-life. All parameters were estimated using the *PKNCA* package in R and then cross-checked  
219 visually using the plots. The half-life was estimated from the best fit line for all available points,  
220 again calculated using this package.

### 221 2.3.4 Population pharmacokinetic analysis

222 Population pharmacokinetic modelling was performed with the software package NONMEM  
223 (version 7.4.1, Icon Development Solutions, Ellicott City, MD).

224 All four metabolites were modelled simultaneously, starting from the structural model illustrated  
225 in Figure 3. MAA formation rate ( $k_f$ , hydrolysis of metamizole) was modelled as a first-order rate,  
226 which was fixed to 20/h (assuming a half-life of 2 min, i.e. complete hydrolysis within 10 min  $\approx$   
227 reported  $t_{max}$  after IV administration) [18]. Both one and two-compartment models were  
228 considered to describe the distribution of metabolites. The apparent volume of distribution was  
229 set to equal values for all metabolites in the absence of IV metabolite administration data and  
230 information on fractions metabolized by different pathways.

231 Between-subject variability was assigned to all structural model parameters and was assumed to  
232 be log-normally distributed. A proportional error model was used for the residual variability.

233 Covariates considered were weight and age. Standard allometric scaling was used to model the  
234 relationship between weight and clearance and volume of distribution (fixed exponents of 0.75  
235 and 1, respectively). The remaining correlation of individual model parameter estimates and  
236 patient demographics was attributed to age, considering (piece-wise) linear, power and sigmoidal  
237 ( $E_{max}$ ) functions based on visual inspection. For sensitivity analyses, see supplement S4.

238 Nested models were compared by the likelihood ratio test ( $\alpha=0.05$ ), based on the NONMEM  
239 objective function value (corresponding to  $-2 \times \log$ -likelihood). Non-nested models were

240 compared by their Akaike information criterion. Further model diagnostics for model  
 241 development and selection included the decrease in inter-individual and residual variability,  
 242 correction in bias of individual random effects over covariates (for shrinkage <20-30%), standard  
 243 error of parameter estimates (target <30%), and goodness of fit plots (observations versus  
 244 predictions, residual diagnostics). The final model was internally evaluated using simulation-  
 245 based diagnostics (visual predictive check,): empirical percentiles (median, 2.5<sup>th</sup> and 97.5<sup>th</sup>  
 246 percentiles) of observed concentrations over time were compared with the 95% CI of simulated  
 247 percentiles.

### 248 2.3.5 Dose evaluation

249 PPK model simulations were performed to (I) evaluate the studied fixed weight-based dosing  
 250 strategy of 10 mg/kg IV, (II) the labelled dose range for 4 weight bands: 50-100 mg for 5-9 kg  
 251 (only IM administration licensed), 100-250 mg for 9-16 kg, 150-400 mg for 16-24 kg, 200-500 mg  
 252 for 24-30 kg (both IM and IV administration licenced), and (III) a new weight-based dosing  
 253 strategy accounting for lower MAA clearance in infants compared to children observed.

254 *Step I.* Deterministic model simulations (including parameter uncertainty) were performed to  
 255 illustrate the model-predicted influence of age and weight on the typical value of MAA total  
 256 clearance ( $TVCL_{MAA,tot}$  = sum of all MAA clearances, eq. 1) and MAA exposure (area under the curve,  
 257  $TVAUC_{0-inf}$ , eq. 2) after a dose of 10 mg/kg. 95% confidence intervals were calculated as 2.5<sup>th</sup> and  
 258 97.5<sup>th</sup> percentiles from 1000 multivariate simulations of the covariance matrix.

$$259 \quad TVCL_{MAA,tot} = TVCL_{MAAtoAA} + TVCL_{MAAtoFAA} + TVCL_{rest} \quad (\text{eq. 1})$$

$$260 \quad TVAUC_{0-\infty} = \frac{D_{metamizole}}{TVCL_{MAA,tot}} \cdot \frac{MW_{MAA}}{MW_{metamizole}} \quad (\text{eq. 2})$$

261 Where  $D_{metamizole}$  is the dose of metamizole in mg (=10 mg/kg · weight in kg), and  $MW_{MAA}$  and  
 262  $MW_{metamizole}$  are the molecular weights of MAA (217.27 g/mol) and metamizole (333.34 g/mol),  
 263 respectively.

264  $TVAUC_{0-inf}$  was illustrated over weight, considering the age-specific weight distribution (3<sup>rd</sup> to 97<sup>th</sup>  
 265 percentiles) according to World Health Organization (WHO) percentile curves for children aged  
 266 3, 6, 12, 18, 24, 48 and 72 months, and was compared to median exposure in healthy adults  
 267 reported after a 500-1000 mg IV dose ( $AUC_{500}$ - $AUC_{1000}$ ).

268 *Step II and III.* Stochastic model simulations (including inter-patient variability) of individual MAA  
 269 total clearance ( $CL_{MAA,tot,i}$ ) and corresponding individual  $AUC_{0-inf,i}$  were performed to illustrate the  
 270 expected exposure distribution (95% prediction intervals) following administration of the  
 271 labelled dose range (II) or a weight-based dosing that accounts for age-dependent MAA clearance

272 observed (III). A dataset of 140'000 children aged 3 to 72 months old (1000 patients for each  
1 273 month and gender) was created according to WHO Box-Cox distribution parameters provided for  
2 274 weight for age.  $CL_{MAA,tot,i}$  was then simulated, and corresponding  $AUC_{0-inf,i}$  derived as described in  
3 275 step I. Pediatric exposures were compared to median exposure in adults with a 500-1000 mg IV  
4 276 dose..  
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## 9 277 **2.4 Assessment of Adverse Events**

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11 278 Incidence, nature, and severity of clinical adverse events and laboratory parameter changes  
12 279 between time of drug administration and 6h post-dose were recorded systematically.  
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# 17 280 **3 RESULTS**

## 20 281 **3.1 Demographics**

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22 282 Due to the lower than expected number of eligible patients for the two younger cohorts 1 and 2,  
23 283 the study was amended and these two cohorts were combined according to ICH-E11 age groups ,  
24 284 with the aim of including 13 patients in the combined cohort [23]. At the end of the two-year study  
25 285 period, 25 patients with at least 1 concentration sample were included, and 19 patients completed  
26 286 the predefined sampling for NCA analysis, 6 infants <24 months (flow-chart: Supplemental Figure  
27 287 S1, demographics: Table 2).  
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## 34 288 **3.2 Pharmacokinetics**

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36 289 Plasma concentration-time profiles of all metabolites are shown in Figure 2.  
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### 39 290 **3.2.1 Reference exposure**

40  
41 291 MAA  $AUC_{ref}$  in adults was 48.9 mg/L\*h (95% CI 44.3, 53.4), resulting in a 80%-125%  $AUC_{ref}$  range  
42 292 of 39.2-61.2 mg/L\*h [8, 12, 18, 19].  $AUC_{1000}$  and  $AUC_{500}$  were 69.9 and 34.9 mg/L\*h.  
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44

### 45 293 **3.2.2 Non-compartmental analysis**

46  
47 294  $AUC_{0-inf}$  and other estimates from NCA are summarized for each cohort in Table 3.  $AUC_{0-inf}$  of MAA  
48 295 in the cohort of children aged 2-6 years was with 29.9 mg/L\*h (95% CI 23.4, 38.2) significantly  
49 296 lower than the 80% limit of  $AUC_{ref}$ .  $AUC_{0-inf}$  of MAA in infants 3-23 months was with 43.6 (95% CI  
50 297 15.8, 119.0) mg/L\*h comparable to  $AUC_{Ref}$ , but the latter showed considerable variability.  
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### 55 298 **3.2.3 Population pharmacokinetic analysis**

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57 299 Two samples with an MAA concentration increase >50% were observed, resulting in the exclusion  
58 300 of one patient (>24 months) for the primary PPK analysis. A one-compartment model was chosen  
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301 to describe the distribution of all metabolites. All metabolic rates were described by first-order  
302 constants ( $=CL/V$ ), there was no evidence of saturable processes. The final structural model is  
303 illustrated in Figure 3.

304 More than half of inter-individual variability in MAA clearance could be explained by the  
305 covariates weight and age ( $CL_{MAAtoAA}$ : decreased from 86% to 52% and 31%;  $CL_{MAAtoFAA}$ : from  
306 112% to 73% and 40%;  $CL_{MAArest}$ : from 184% to 151% and 54%, Supplemental Figure S4.1). Both  
307 a piece-wise linear and power model with age could describe the observed lower weight-  
308 corrected clearance in patients <24 months (corresponding to the time when most enzyme  
309 maturation processes are considered complete, and time where no age-dependency could be  
310 observed in the present dataset) [24]. As final model a “piece-wise” power relationship with age  
311 was chosen (lowest OFV, exclusion of negative values in simulations):

$$312 \quad CL_{TV} = \theta_1 \cdot \left(\frac{weight}{15}\right)^{0.75} \cdot \left(\frac{age}{24}\right)^{\theta_{age}} \text{ for age } < 24 \text{ months, and}$$

$$313 \quad CL_{TV} = \theta_1 \cdot \left(\frac{weight}{15}\right)^{0.75} \text{ for age } \geq 24 \text{ months}$$

314 where  $CL_{TV}$  is the typical clearance parameter for the given covariates weight and age,  $\theta_1$  is the  
315 typical clearance for a patient with weight = 15 kg (median in the analysed dataset) and age  $\geq$  24  
316 months, weight is given in kg, age in months.

317 A similar age relationship was also observed with  $CL_{FAAother}$  (exponent: 0.84, RSE: 26%; BSV  $\rightarrow$  0)  
318 and V (exponent: 0.51, RSE: 21%; BSV decrease by 35%) in infants <24 months (Supplemental  
319 Figure S4.2), but was not included in the final model (no influence on MAA total clearance  
320 estimate; unclear physiologic meaning of lower weight-adjusted volume in younger children -  
321 rather the opposite would be expected from a hydrophilic drug). Large inter-patient variability in  
322 metabolic clearance of AA to AAA (mediated by polymorphic *NAT2*) could be explained by a latent  
323 variable, corresponding to a slow or fast metabolizer phenotype ( $\approx$ 7 times faster clearance  
324 estimated in patients assigned to the rapid metabolizer, frequency of slow metabolizers estimated  
325 to 26%), which was not measured in the present study [12].

### 326 3.2.4 Model evaluation

327 Residual diagnostics and VPCs are illustrated in the Supplement (Figures S4.3-S4.4). VPC suggests  
328 good agreement between observed and simulated percentiles. Residual diagnostics indicate  
329 unbiased predictions of MAA, while some bias for other metabolites remained, which was  
330 considered acceptable, given the main purpose of the study, and satisfying VPC diagnostics.  
331 Parameter estimates of the final selected model are summarized in Table 4.

### 332 3.3 Dose evaluation

1  
2 333 Figure 4 illustrates model-predicted  $TVAUC_{0-inf}$  with 95%CI over weight for different ages;  
3  
4 334 corresponding  $TVCL_{MAA,tot}$  and individual NCA and PPK  $AUC_{0-inf}$  estimates are shown in the  
5  
6 335 Supplement (Figures S5.1-S5.2). Supplemental Figure 5.2 illustrates the expected exposure  
7  
8 336 distribution for the labelled dose range (while for <1 year only IM administration is licensed), and  
9  
9 337 for a weight-based dosing scheme accounting for lower clearance in infants.

### 11 338 3.4 Safety

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14 339 AE were fever (n=4), nausea (n=1), vomiting (n=1), abdominal pain (n=1) and pain at the surgical  
15  
16 340 site (n=1), all of which were classified mild to moderate and unlikely related to the study drug.  
17  
18 341 There were no clinically significant changes in hematology and biochemistry parameters before,  
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20 342 and 6h after, the administration of metamizole (see Supplement S3). No clinically significant drop  
21  
22 343 in blood pressure requiring treatment was recorded. No serious adverse event occurred during  
23  
24 344 the study. No patient developed agranulocytosis within the study period.

## 26 345 4 DISCUSSION

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29 346 This is the first study that describes the pharmacokinetics of the main metabolites of metamizole  
30  
31 347 after IV administration in infants and children younger than 6 years of age. After a single IV dose  
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33 348 of 10 mg/kg, children aged 2-6 years had a significantly (39%) lower exposure ( $AUC_{0-inf}$ ) than the  
34  
35 349 80% limit of adult  $AUC_{Ref}$  for the active metamizole metabolite MAA, suggesting that children  
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37 350 receiving the recommended 10 mg/kg dose may be slightly under-dosed compared to a 70 kg  
38  
39 351 adult receiving the same weight-based dose (700 mg for a 70 kg adult). On the other hand, infants  
40  
41 352 <2 years had comparable average exposure to adults, with a large (~10-fold) variability in MAA  
42  
43 353  $AUC_{0-inf}$ . Increased MAA concentrations were measured in infants <1 year, suggesting that they  
44  
45 354 may be overdosed when receiving same weight-based IV doses. PPK modeling and simulation  
46  
47 355 demonstrated that a dose of 5 mg/kg in infants <1 year and 10-20 mg/kg in children 1-6 years  
48  
49 356 would achieve a more consistent exposure in infants and young children compared to that  
50  
51 357 observed in adults at the approved dose of 500-1000 mg (corresponding to 7-14 mg/kg for a 70  
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53 358 kg adult). Considering a weight range of 50-100 kg in adults, such dose recommendations would  
54  
55 359 lie within the corresponding adult weight-adjusted dose range of 5-20 mg/kg.

56 360 It has been suggested before that MAA metabolism occurs faster in children >1 year than in adults  
57  
58 361 by Balogh et al., who studied 38 children aged 1-11 years after a single oral dose of metamizole (8  
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60 362 mg/kg) compared to healthy adults. Urinary excretion of the metabolites AA, FAA and AAA within  
61  
62 363 6h was significantly higher in younger children than in adults, but plasma concentrations were

364 unfortunately not measured in their study [17]. In line with those findings, plasma  $C_{max}$  of those  
1 365 metabolites tended to be lower and  $t_{max}$  tended to be earlier in our study (Table 3), compared to  
2 366 mean values reported in adults after an IV dose of 1g (AA: 1.5-1.6 mg/L and 3.1-4.8 h, AAA: 1.4-  
3 367 1.6 mg/L and 13-17.3 h, FAA: 1.4 mg/L and 7.2-8.2 h) [8]. No pharmacokinetic data in infants <1  
4 368 year is available to compare our findings of slower metabolism in this age group. However, our  
5 369 results are in line with lower CYP activity seen in young children during the first 1-2 years of life.  
6 370 CYP specific isoforms, including CYP2C19, show developmental expression patterns that can  
7 371 affect drug metabolism [24-27].

14 372 Model-predicted MAA clearance for a 70 kg adult (167 mL/min) is in excellent agreement with  
15 373 reported values, suggesting usefulness of the model for extrapolation to older children [8]. Model-  
16 374 derived average half-lives for a 70 kg adult are as follows: MAA: 3.2 h, AA 10.5 h (slow  
17 375 metabolizers) and 1.4 h (fast metabolizers), AAA: 3.7 h and FAA: 5.6 h. Those extrapolated half-  
18 376 lives of active metabolites MAA and AA are in line with data reported in adults [12]. Predicted AAA  
19 377 and FAA (non-active metabolites) half-lives are shorter than reported from NCA, likely because of  
20 378 limited data available for the elimination phase of those metabolites [8]. The discrepancy may  
21 379 potentially also indicate age-dependent elimination in children that the model did not account for,  
22 380 and limited usefulness of the model for extrapolation of the pharmacokinetics of inactive  
23 381 metabolites. Data suggest potential for considerable accumulation of MAA in infants <1 year and  
24 382 of other metabolites (AA in slow metabolizers, AAA and FAA; exposure  $\approx$ 10% of MAA, Figure 2)  
25 383 after multiple dosing. The relevance of AA, AAA and FAA for drug safety and efficacy is not well  
26 384 described. Additional clinical studies are needed to characterize multiple-dose pharmacokinetics  
27 385 and safety of metamizole in infants. Because of these uncertainties, use of metamizole should be  
28 386 limited to short-term use, or may be completely avoided in infants <1 year.

40 387 *NAT2* genotypes were not determined in this study, but presence of two phenotypes (26% slow  
41 388 and 74% fast metabolizers) was suggested. Since age appeared unrelated to the metabolic activity,  
42 389 we may assume that maturation of this enzyme already is high in infants >3 months (no age-  
43 390 relationship shown in this study). Literature suggests that *NAT2* genotypes may even be grouped  
44 391 into three phenotypes, but many pharmacokinetic studies have reported two phenotypes only  
45 392 (e.g. for sulfamethoxazole, isoniazide or caffeine)[28].

51 393 Therapeutic efficacy and concentration-dependency could not be evaluated in our study due to  
52 394 concomitant use of standard analgesic combination therapy. Effectiveness of our recommended  
53 395 dose of 10-20 mg/kg for children >1 year is however supported by studies having demonstrated  
54 396 effective pain relief in children after a dose of 15 mg/kg. [14, 15] . Our single dose study in a small  
55 397 number of children does also not allow characterization of the safety profile of metamizole, or  
56 398 evaluation of dose-dependency of AE in infants and children. Recorded AEs were deemed not

399 related to the study drug, due to the latency time between drug administration and AE occurrence,  
1 400 and alternative explanations for the AEs by the surgical procedures or administered co-  
2 401 medications. The use of metamizole is controversial due to its risk of agranulocytosis [29-31].  
3 402 With an incidence rate of 0.46-1.63 cases per million person-days, and approximately 4% of  
4 403 reported cases in patients <19 years, the probability for observing such a severe AE in our study  
5 404 was very low [32-34]. Also, the probability to observe serious hemodynamic, anaphylactic or  
6 405 respiratory adverse AE was low (estimated incidence <0.3% after a single IV dose of metamizole)  
7 406 [35]. A recent adult study further reported a dose-dependent risk of acute kidney injury in an  
8 407 intensive care unit, which has not yet been studied in children [36]. As aforementioned, there are  
9 408 uncertainties regarding accumulation and pharmacological safety properties, especially in infants  
10 409 < 1 year. For these reasons we recommend to limit administration to 1 or 2 days. If administered  
11 410 over several days regular monitoring for clinical and laboratory abnormalities is warranted [37].

20  
21 411 Since only 4 infants below the age of 1 year could be included in this study, there remains  
22 412 uncertainty about the exact optimal dose for this age group (as illustrated by 95%CI in Figure 4).  
23 413 The requirement for dose reduction was still perceived highly appropriate for this age group, due  
24 414 to highest MAA exposure ( $\approx$ 2-fold higher than  $AUC_{1000}$ ) observed in these patients and plausible  
25 415 maturation of metabolic enzymes. For older children aged 2-6 years, there is some uncertainty  
26 416 concerning the appropriate reference weight for scaling of  $AUC_{ref}$  (weight of healthy volunteers  
27 417 not reported in all studies). For a lower adult reference weight (reported range: 54-68kg), the  
28 418 relative difference to adults exposure would be slightly lower than the calculated 39% [8, 12, 18,  
29 419 19]. It also has to be noted that  $AUC_{0-inf}$  estimates from NCA tended to be lower than from PPK,  
30 420 which is to be expected, since higher peak concentrations are assumed to occur within 10 min  
31 421 after IV administration in PPK analysis compared to those measured with the first sample at 1h  
32 422 post-dose (with the sampling scheme being designed to describe the elimination phase). The  
33 423 proposed doses for both age groups are hence also based on practical considerations, targeting a  
34 424 simple dosing scheme, which may reduce dosing errors.

35 425 We consider that polymorphisms of genes encoding for the enzymes involved in drug metabolism  
36 426 might have contributed to the above-mentioned variability. Genotyping of these enzymes,  
37 427 however, was not a goal of this study, and sample size of this pharmacokinetic study would be too  
38 428 small to draw valid conclusions.

39 429 In conclusion, this prospective single dose study reports for the first time plasma  
40 430 pharmacokinetics data of IV metamizole in infants and children up to 6 years old. Body weight-  
41 431 adjusted dosing in children, assuming a linear relationship between weight and dose, is arbitrary  
42 432 and does not account for any specific differences in drug pharmacokinetics between children of  
43 433 different ages and adults. Significant age-dependency of the elimination kinetics of the main active

434 metabolite MAA was found, resulting in higher exposure in infants <1 year compared to older  
1 435 children and adults. This suggests the need for a reduced weight-based (off-label) IV dose in  
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3 436 infants <1 year compared to older children up to 6 years (5 mg/kg versus 10-20 mg/kg) to achieve  
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5 437 equivalent adult exposure, and mitigate the risk for overdosing in young infants. Additional  
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7 438 clinical studies are warranted to further evaluate efficacy and safety of proposed dosing in infants.

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440 **COMPLIANCE WITH ETHICAL STANDARDS**

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441 **CONFLICT OF INTEREST**

442 V.C.Z.: none

443 F.R.: none

444 A.A.: none

445 V.G.: none

446 C.B.: none

447 J.A.B.: Husband is senior corporate counsel at Novartis International AG, Basel, Switzerland, and  
448 holds Novartis stock and stock options.

449 M.H.: none

450 T.O.E.:

451 U.D.: none

452 F.B.: none

453 N.G.: none

454 S.H.-C.: none

455 J.N.v.d.A.: none

456 M.P. is part-time consultant for Certara, L.P..

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463 **ETHICAL APPROVAL**

464 All procedures performed in studies involving human participants were in accordance with the  
465 ethical standards of the national research committee and with the 1964 Helsinki declaration and  
466 its later amendments or comparable ethical standards.

467 **INFORMED CONSENT**

468 Informed consent was obtained from all individual participants included in the study.

469 AUTHOR CONTRIBUTIONS

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470 F.R., M.P., A.A., T.O.E., M.H., N.G. and J.N.v.d.A. designed the research; V.C.Z., F.R., and J.A.B. performed  
471 the research; A.A., V.G., C.B., U.D., F.B. and V.Z. analyzed the data; M.H., U.D. and F.B. performed the  
472 bioanalysis; V.C.Z., F.R., V.G. and M.P. wrote the manuscript, J.N.v.d.A, T.O.E., M.H., N.G. and S.H.-C.  
473 critically revised the manuscript. All authors reviewed and approved the final version of the  
474 manuscript before submission.

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575 **6 TABLES**

576 **Table 1:** Licensed parenteral dosing of metamizole (Novalgine®, 500 mg/mL, solution for  
 577 injection) for children <6 years and adults. In children <1 year only IM administration is  
 578 recommended. Injection may be repeated after 6-8 h.

Body weight	Route of administration	Single dose	Corresponding calculated weight-based dose range <sup>a</sup>
5-8 kg	Only IM	0.1-0.2 mL = 50-100 mg	6.2-20.0 mg/kg
9-15 kg	IM or IV	0.2-0.5 mL = 100-250 mg	6.7-27.8 mg/kg
16-23 kg	IM or IV	0.3-0.8 mL = 150-400 mg	6.5-25.0 mg/kg
24-30 kg	IM or IV	0.4-1.0 mL = 200-500 mg	6.7-20.8 mg/kg
<i>Adults</i>			
50-100 kg	IM or IV	1-2 mL = 500-1000 mg (max. single dose 5 mL = 2500 mg, max. daily dose: 5000 mg)	10-20 mg/kg (max. single dose 25- 50 mg/kg, max. daily dose 50-100 mg/kg)

579 IM: intramuscular; IV: intravenous.

580 <sup>a</sup> calculated as: minimal recommended single dose / upper limit of body weight range = minimal  
 581 weight based dose and maximal recommended single dose / lower limit of body weight range =  
 582 maximal weight based dose.

583

584 **Table 2:** Patient demographics. Continuous variables are given as median and interquartile  
 1 585 range (IQR) for all patients with at least 1 concentration sample.

	<b>Infants 3-11 months</b> (cohort 1)	<b>Infants 12-23 months</b> (cohort 2)	<b>Children 2-6 years</b> (cohort 3)
<b>Number of individuals (n)</b>			
- with at least 1 concentration sample <sup>a</sup>	4	4	17
- with at least 5 predefined samples <sup>b</sup>	3	3	13
<b>Gender</b>	3 m, 1 f	4 m	11 m, 6 f
<b>Age (months)</b>	8 (6.5; 9.3)	20.5 (17.8; 22.0)	56 (43; 64)
<b>Weight (kg)</b>	8.9 (8.5; 9.7)	11.5 (10.8; 12.0)	17 (15; 19)
<b>z-score weight (for age)</b>	0.58 (0.41;1.10)	0.14 (-0.08; 0.31)	-0.09 (-0.83; 0.45)
<b>Type of surgery (n)</b>	Urologic (3), other (1)		ENT (12), urologic (3), other (2)

27 586 <sup>a</sup> all individuals included in population pharmacokinetic analysis.

29 587 <sup>b</sup> included in non-compartmental analysis.

31 588

589 **Table 3.** Non-compartmental analysis. Pharmacokinetic parameters of the metamizole  
 1 590 metabolites after a single intravenous dose of 10 mg/kg metamizole.

	<b>Infants 3-23 months</b> (n=6)	<b>Children 2-6 years</b> (n=13)
<b><i>MAA (main active metabolite)</i></b>		
AUC <sub>0-inf</sub> (mg/L*h) <sup>a</sup>	43.6 (15.8, 119.0)	29.9 (23.4, 38.2)
AUC <sub>0-λ</sub> (mg/L*h) <sup>a</sup>	31.7 (14.8, 67,9)	22.7 (19.5, 26.5)
C <sub>1h</sub> (mg/L) <sup>b</sup>	10.6 [8.3, 15.0]	7.8 [6.5, 9.4]
t <sub>max</sub> (h)	1	1
t <sub>1/2</sub> (h) <sup>b</sup>	2.4 [1.7, 3.9]	2.0 [1.9, 3.1]
λ <sub>z</sub> (h <sup>-1</sup> ) <sup>b</sup>	0.3 [0.2, 0.4]	0.3 [0.2, 0.4]
<b><i>Metabolite AA</i></b>		
AUC <sub>0-λ</sub> (mg/L*h) <sup>a</sup>	3.6 (2.0, 6.4)	3.1 (2.5, 3.9)
C <sub>max</sub> (mg/L) <sup>b</sup>	0.8 [0.6, 0.9]	0.6 [0.6, 1.0]
t <sub>max</sub> (h) <sup>b</sup>	2.0 [2.0, 3.3]	2.0 [2.0, 4.0]
<b><i>Metabolite AAA</i></b>		
AUC <sub>0-λ</sub> (mg/L*h) <sup>a</sup>	4.6 (2.0, 10.9)	3.3 (2.0, 5.4)
C <sub>max</sub> (mg/L) <sup>b</sup>	1.6 [0.8, 1.8]	1.2 [0.7, 1.5]
t <sub>max</sub> (h) <sup>b</sup>	6.0 [5.9, 6.0]	6.0 [5.8, 6.0]
<b><i>Metabolite FAA</i></b>		
AUC <sub>0-λ</sub> (mg/L*h) <sup>a</sup>	5.7 (4.4, 7.4)	5.1 [4.0, 6.6]
C <sub>max</sub> (mg/L) <sup>b</sup>	1.4 [1.3, 1.5]	1.3 [0.9, 1.4]
t <sub>max</sub> (h) <sup>b</sup>	4.0 [4.0, 4.0]	5.8 [4.0, 6.0]

591 AUC<sub>0-inf</sub> area under the plasma-concentration time curve from 0 to infinity; C<sub>1h</sub> plasma  
 592 concentration 1h after dosing; C<sub>max</sub> maximal plasma concentration; T<sub>max</sub> time of C<sub>max</sub>; t<sub>1/2</sub>  
 593 elimination half-life; λ<sub>z</sub> terminal elimination rate constant

594 <sup>a</sup> presented as geometric mean (95% confidence interval).

595 <sup>b</sup> presented as median [interquartile range];



598 **Table 4:** Estimates of population pharmacokinetic model.

Parameter	Estimate (RSE)	Inter-individual variability (RSE)
<b>Structural kinetic model</b>		
$k_h$ (1/h)	20 (fixed)	-
V (L) for 15 kg <sup>a</sup>	9.98 (5%)	21.6% (18%)
CL <sub>MAAtoAA</sub> (L/h) for 15 kg <sup>b,c</sup>	1.07 (11%)	38%* (18%)
CL <sub>MAAtoFAA</sub> (L/h) for 15 kg <sup>b,c</sup>	0.844 (13%)	51%* (17%)
CL <sub>MAAtoOther</sub> (L/h) for 15 kg <sup>b,c</sup>	1.26 (14%)	45% (21%)
CL <sub>AAtoAAA fast</sub> (L/h) for 15 kg <sup>b</sup>	7.46 (14%)	51% (18%)
CL <sub>AAtoAAA slow</sub> (L/h) for 15 kg <sup>b</sup>	0.972 (27%)	(same)
Proportion of slow metabolizers	0.259 (39%)	-
CL <sub>AAA</sub> (L/h) for 15 kg <sup>b</sup>	2.72 (11%)	39% (23%)
CL <sub>FAA</sub> (L/h) for 15 kg <sup>b</sup>	1.83 (8%)	25% (24%)
<b>Covariate model for age &lt;24 months</b>		
$\theta_{age,MAAtoAA}$ [-]	0.663 (29%)	
$\theta_{age,MAAtoFAA}$ [-]	0.969 (25%)	
$\theta_{age,MAAtoOther}$ [-]	2.39 (24%)	
<b>Error model</b>		
$\epsilon_{MAA}$ proportional (%)	23% (10%)	
$\epsilon_{AA}$ proportional (%)	13% (9%)	
$\epsilon_{AAA}$ proportional (%)	19% (11%)	
$\epsilon_{FAA}$ proportional (%)	10% (9%)	

599 RSE: relative standard error. \*estimated correlation: 96% (RSE: 36%). <sup>a</sup>allometrically scaled and  
600 centered to 15 kg:  $V_{TV} = V \cdot (\text{weight}/15)^1$ . <sup>b</sup>allometrically scaled and centered to 15 kg:  $CL_{TV} = CL \cdot$   
601  $(\text{weight}/15)^{0.75}$ . <sup>c</sup>age as covariate included as follows for age <24 months:  $CL_{TV} = CL \cdot$   
602  $(\text{weight}/15)^{0.75} \cdot (\text{age}/24)^{\theta_{age}}$ . CV: coefficient of variation calculated as  $\sqrt{(\omega^2-1)}$ , where  $\omega^2$  is the  
603 variance of log-normally distributed interindividual variability.

605 **7 FIGURES**

606 **Figure 1:** The metabolism of metamizole and its major metabolites

607  
608 **Figure 2:** Measured individual concentration-time profiles of all metamizole metabolites. Three  
609 age groups are differentiated by color: <1 year (4 patients aged 5-10 months, among 3 with  $\geq 5$   
610 samples), 1 year old (4 patients aged 14-22 months, among 3 with  $\geq 5$  samples), and 2-6 years (17  
611 patients aged 28-70 months, among 13 with  $\geq 5$  samples). *X*: MAA concentrations increasing  $>50\%$   
612 from its previous value (physiologically not plausible and excluded in PPK analysis, but included  
613 in NCA). *Dashed horizontal lines*: lower limit of quantification (LLOQ). Concentrations measured  
614 below LLOQ are plotted at  $LLOQ/2$ .

615  
616 **Figure 3:** Illustration of structural model of metamizole and its metabolites considered. Initially,  
617 all metabolic pathways (arrows) reported by Levy et al. [8] were considered. Grey dashed arrows  
618 indicate pathways that were not identifiable in this modelling work.  $k_H$ : first-order hydrolysis rate.  
619  $CL_{MAAtoAA}$ ,  $CL_{MAAtoAAA}$ ,  $CL_{AAtoFAA}$ ,  $CL_{AAtoAAA}$ : metabolic clearances.  $CL_{MAAOther}$ ,  $CL_{AAOther}$ ,  $CL_{AAAOther}$ ,  $CL_{FAAOther}$ :  
620 sum of other clearance routes. Modelling work focussed on unbiased description of MAA, the main  
621 active metabolite of the prodrug metamizole. Volumes of distribution for all metabolites were  
622 assumed to be equal in the absence of data on single IV metabolite administration.

623  
624 **Figure 4:** Illustration of model-predicted typical AUC for patients of different age and weight  
625 with 95% confidence intervals (shaded areas), receiving an intravenous (IV) dose of metamizole  
626 of 10 mg/kg. Weight for age bands were simulated according to WHO percentiles curves  
627 (extending from 3<sup>rd</sup> to 97<sup>th</sup> percentiles). *Black horizontal lines*: reference AUC in healthy  
628 volunteers receiving a dose of 500 mg or 1000 mg metamizole ( $AUC_{500}$ ,  $AUC_{1000}$ ). *Dashed*  
629 *horizontal line*: 2-fold increase in  $AUC_{1000}$ .

630  
631 **Figure 5:** Illustration of model-predicted distribution of individual  $AUC_{0-inf}$  for patients of  
632 different age (1000 individuals per month of age and gender simulated). *Left*: exposure following  
633 labelled dosing (Table 1, for 5-9kg only IM administration is licensed). *Right*: exposure following  
634 a new proposed weight-based IV dosing strategy for children 3-11 months and 1-6 years. *Dashed*  
635 *lines*: median. *shaded area*: 90% prediction interval.



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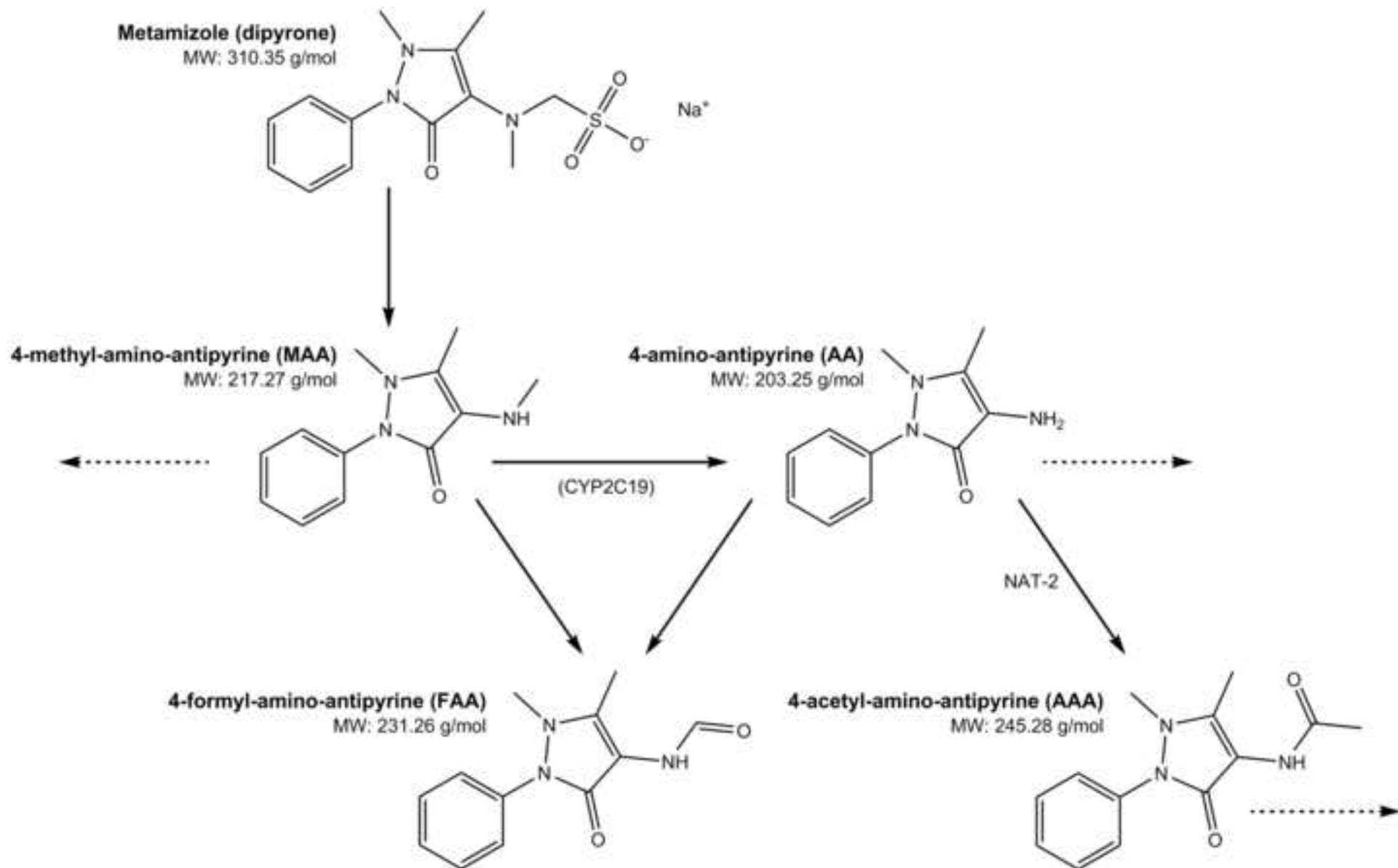


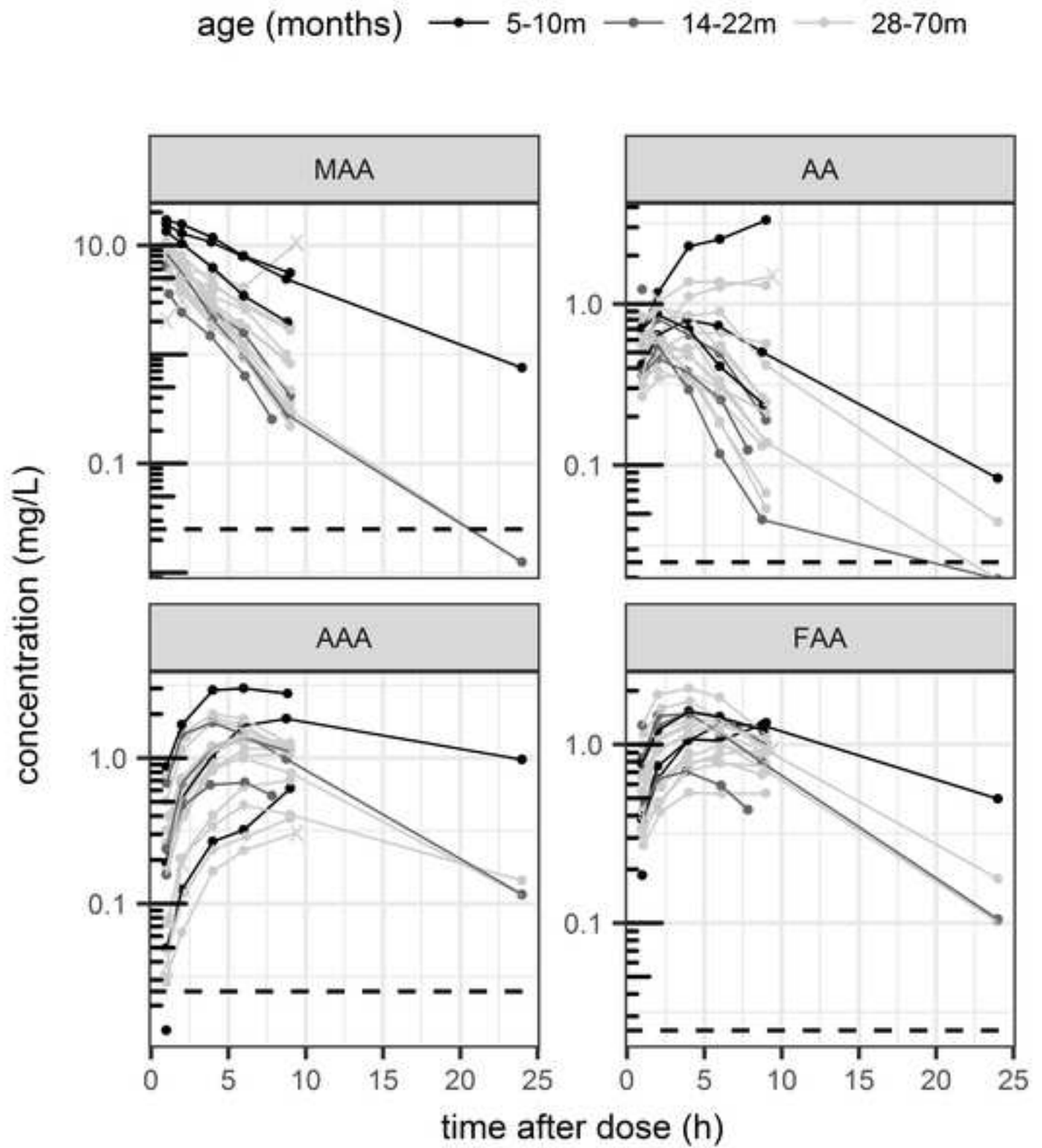


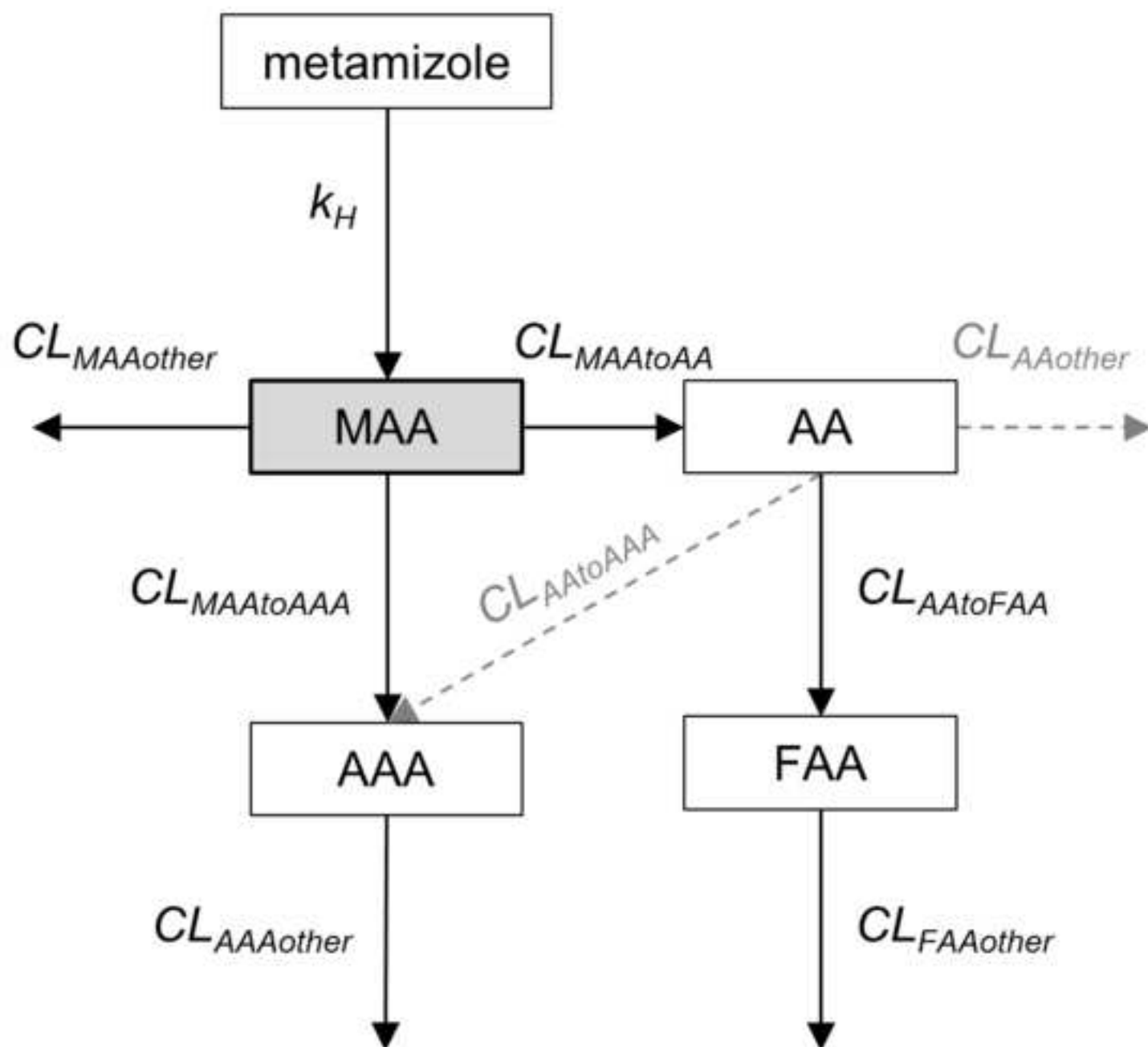
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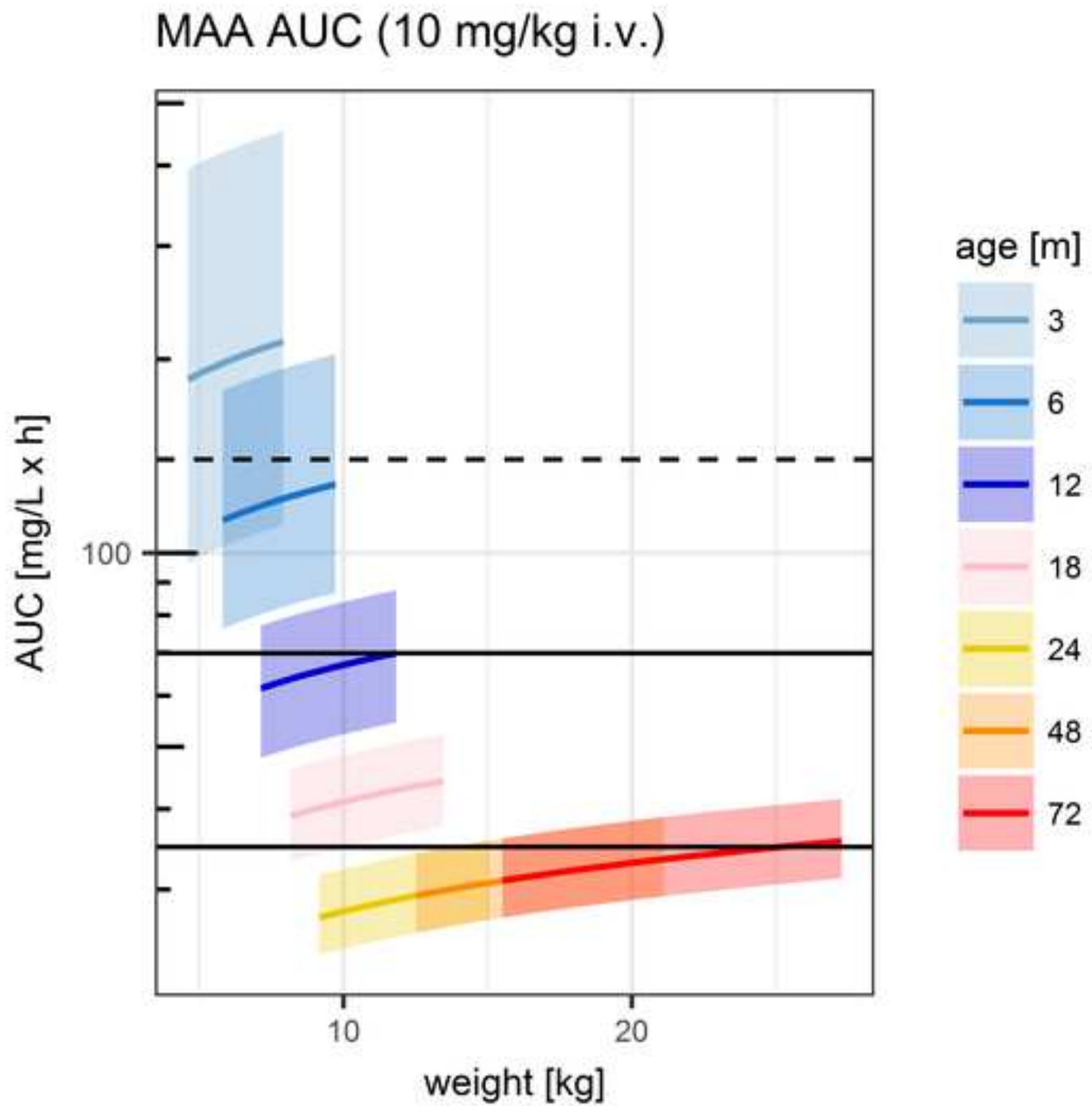
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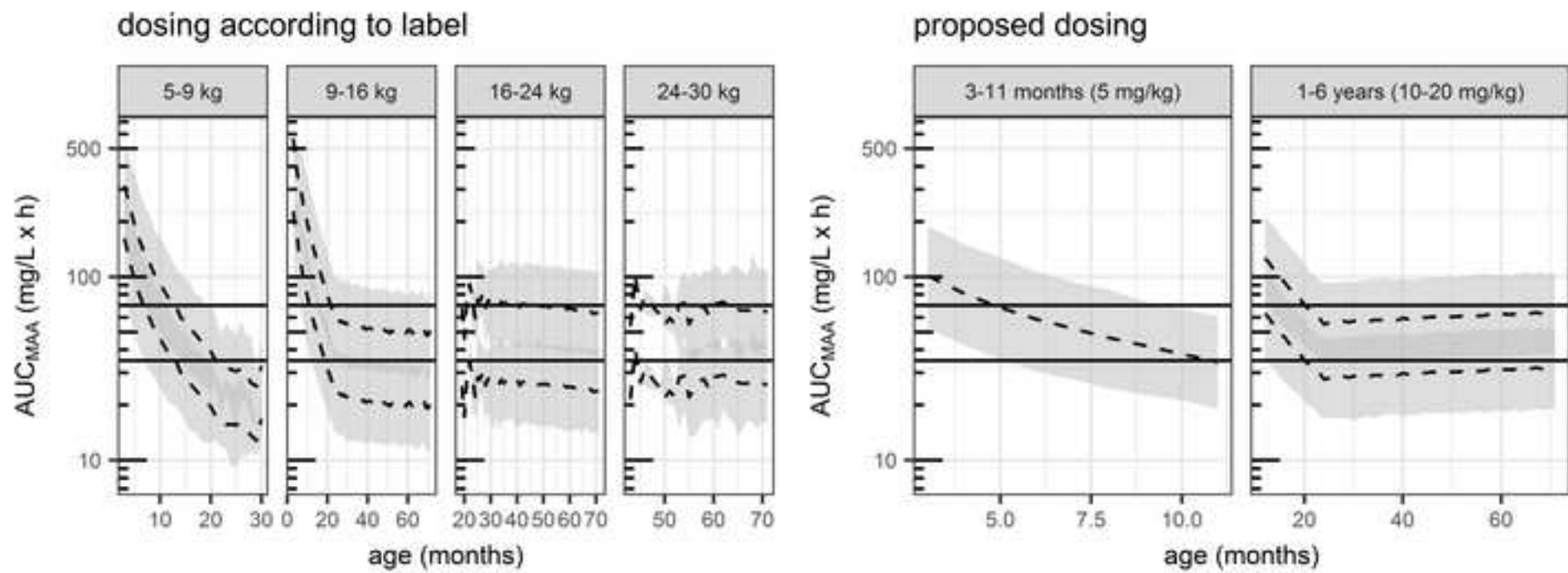














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