Microdosing: An opportunity for safer drug development in children?

Saskia N. de Wildt

Professor of Clinical Pharmacology
Pediatric Intensivist-Clinical Pharmacologist

Erasmus MC
Universitair Medisch Centrum Rotterdam

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Magnitude of the problem

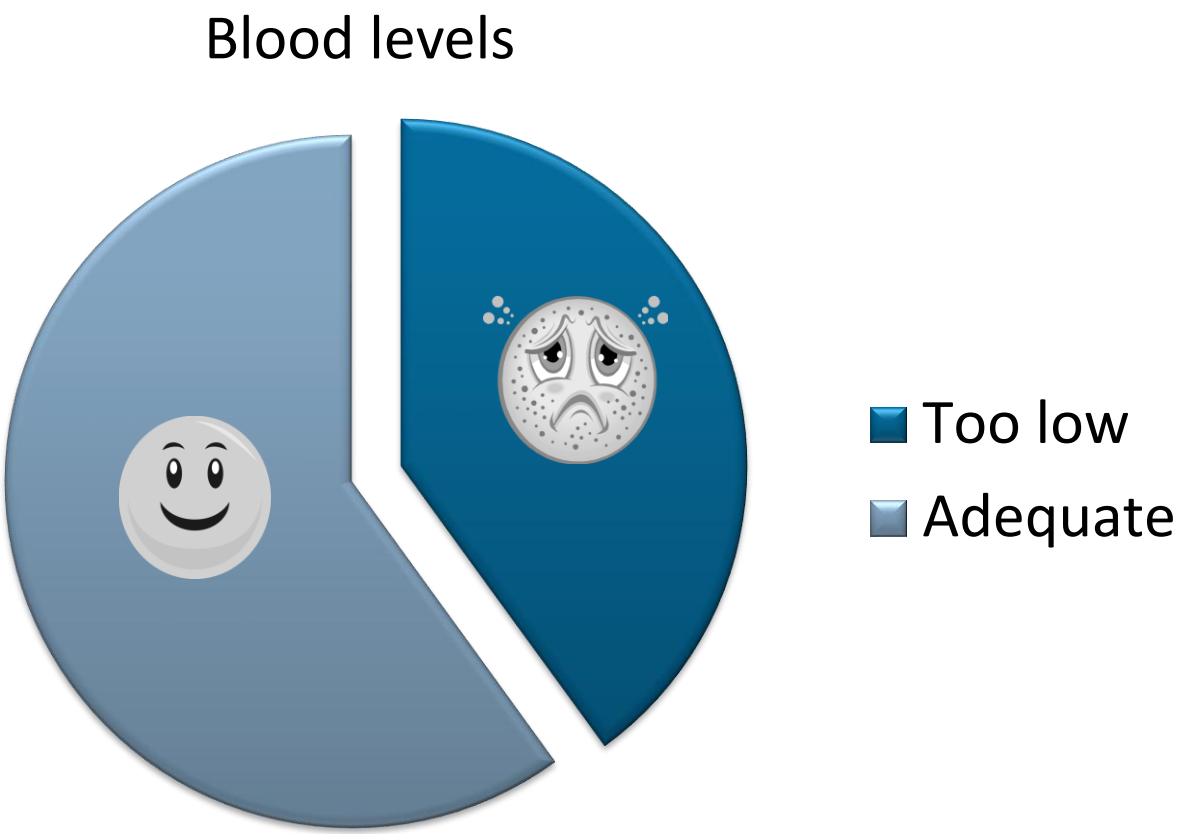
't Jong et al NEJM 2000, BMJ 2002, Pediatrics 2000

Fatalities in children

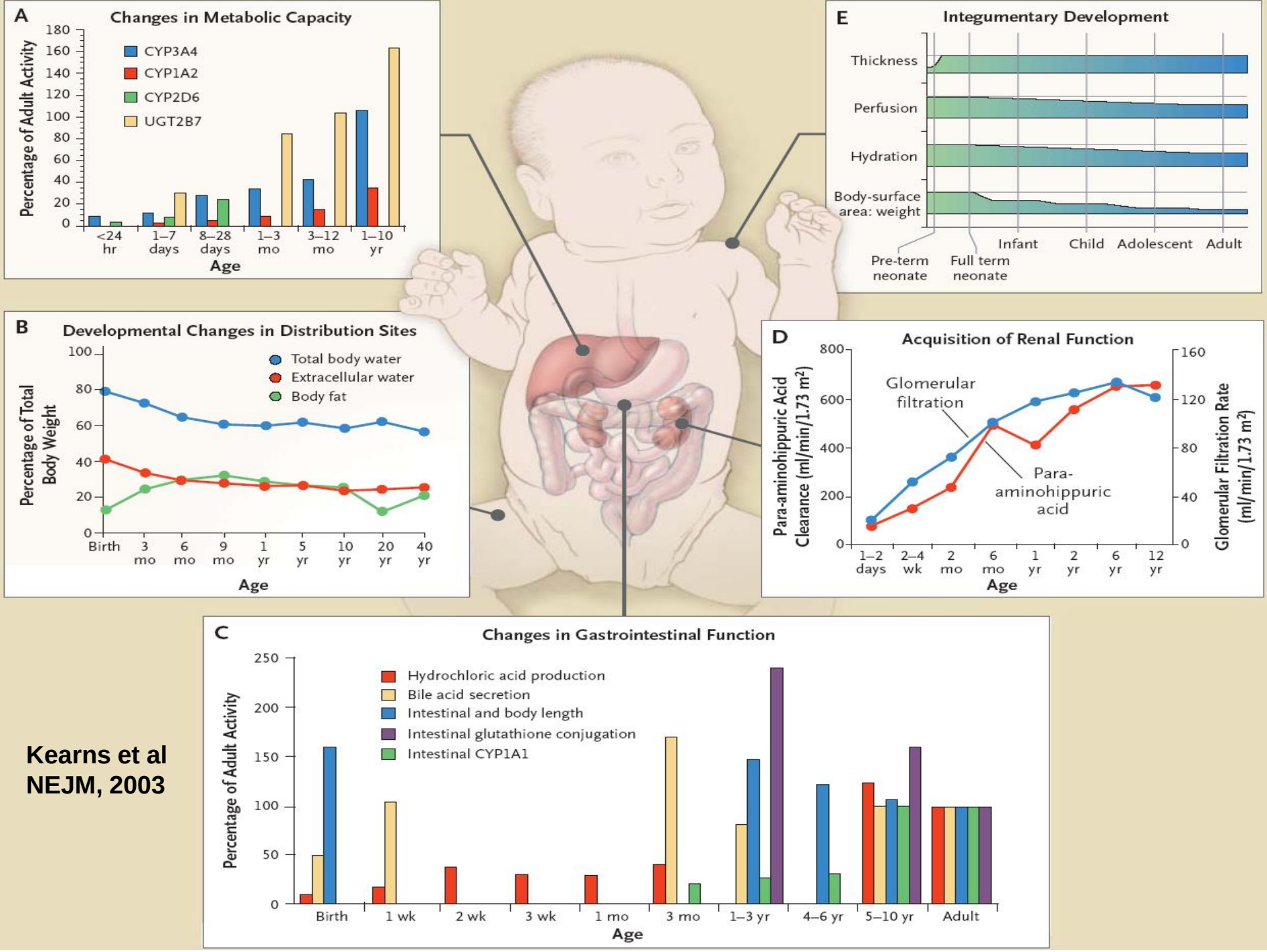
1959

2007

Drug failure – HIV example



Van Rossum, Fraaij, de Groot Lancet ID, 2002



Kearns et al NEJM, 2003

Microdosing: smart solution?

- Microdose
  - 1/100 of therapeutic dose
  - or max 100 µg
  - ± Radioactive label: ^{14}C

- Drug levels with LC-MS or AMS

- FDA/EMA supported

Dose linearity important

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Microdose Study of ^{14}C-Acetaminoph With Accelerator Mass Spectrometry to Examine Pharmacokinetics of Parer and Metabolites in Healthy Subjects

Z Tozuka[1], H Kusuhara[2], K Nozawa[1], Y Hamabe[3], I Ikushima[4], T Ikeda[5] and Y S

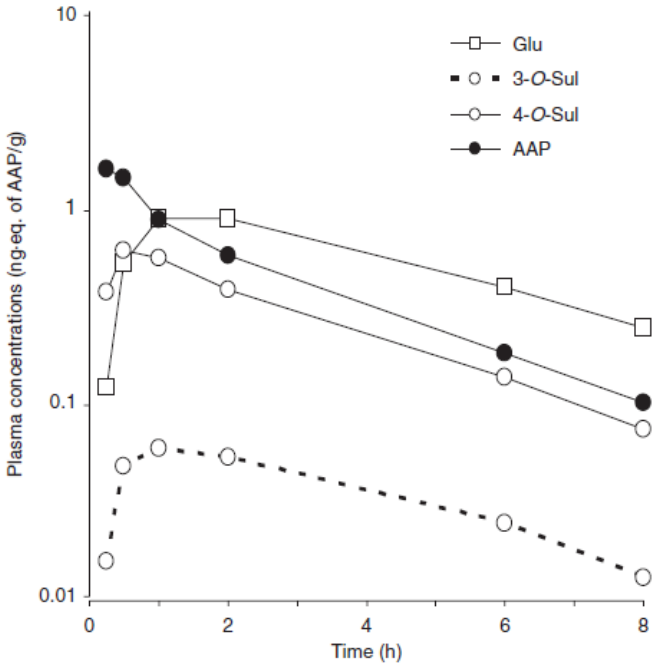
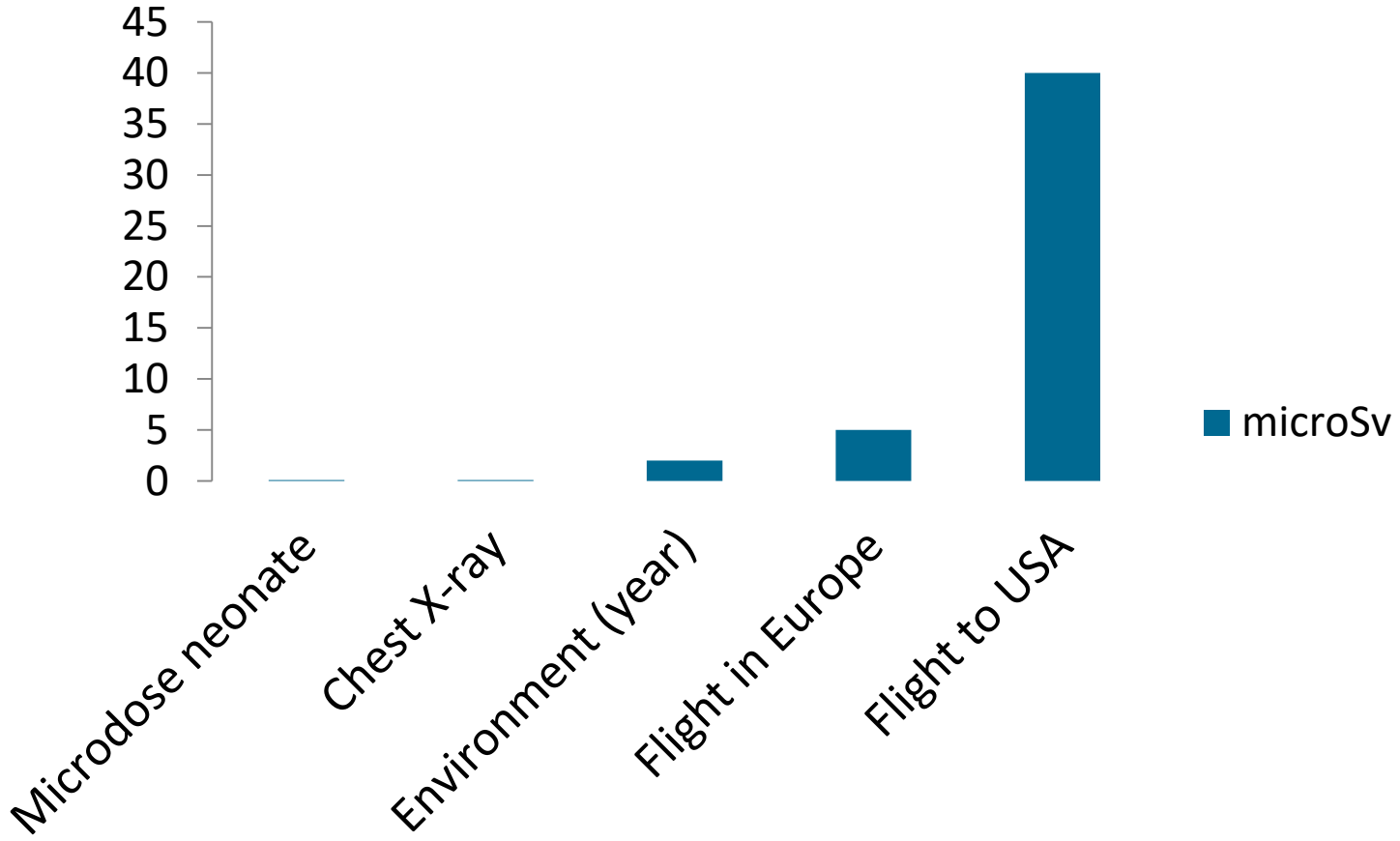


Figure 4 Time profiles of AAP and its metabolites in the pooled plasma of six subjects after oral administration of ^{14}C-AAP. Pooled plasma specimens collected at 0.25, 0.5, 1, 2, and 8 h were subjected to LC-AMS analysis. 3-*O*-Sul, AAP-3-hydroxysulfate; 4-*O*-Sul, AAP-4-hyroxylsulfate; AAP, acetaminophen; Glu, AAP-glucuronide; LC-AMS, liquid chromatography–accelerator mass spectrometry.

Radioactivity in kids?

Radiation comparison



Paracetamol as probe for UGT and ST

Paracetamol
(AAP)

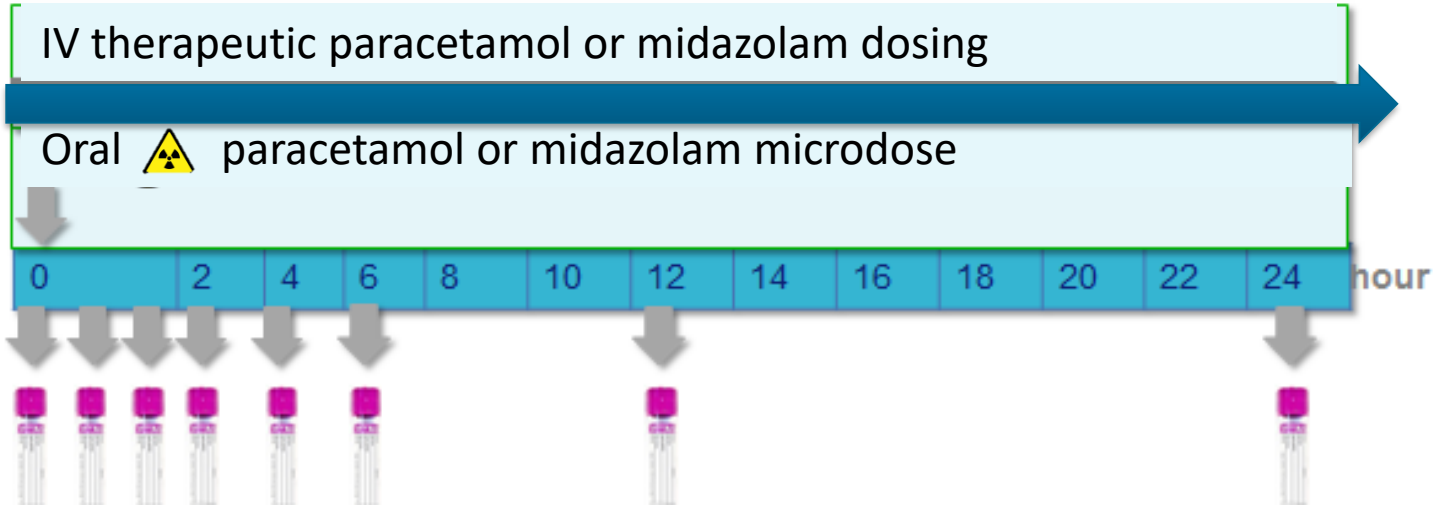
- **Glucuronidation**
- **Sulphation**
- CYP + GSH conjugation

Neonate	**Neonate**	**Infant**	**Toddler**	**Child**
Birth – 10 days	11 days– 1 mth	1 – 6 mth	6 mth – 2 yr	2 – 6 yr

Study aim and design

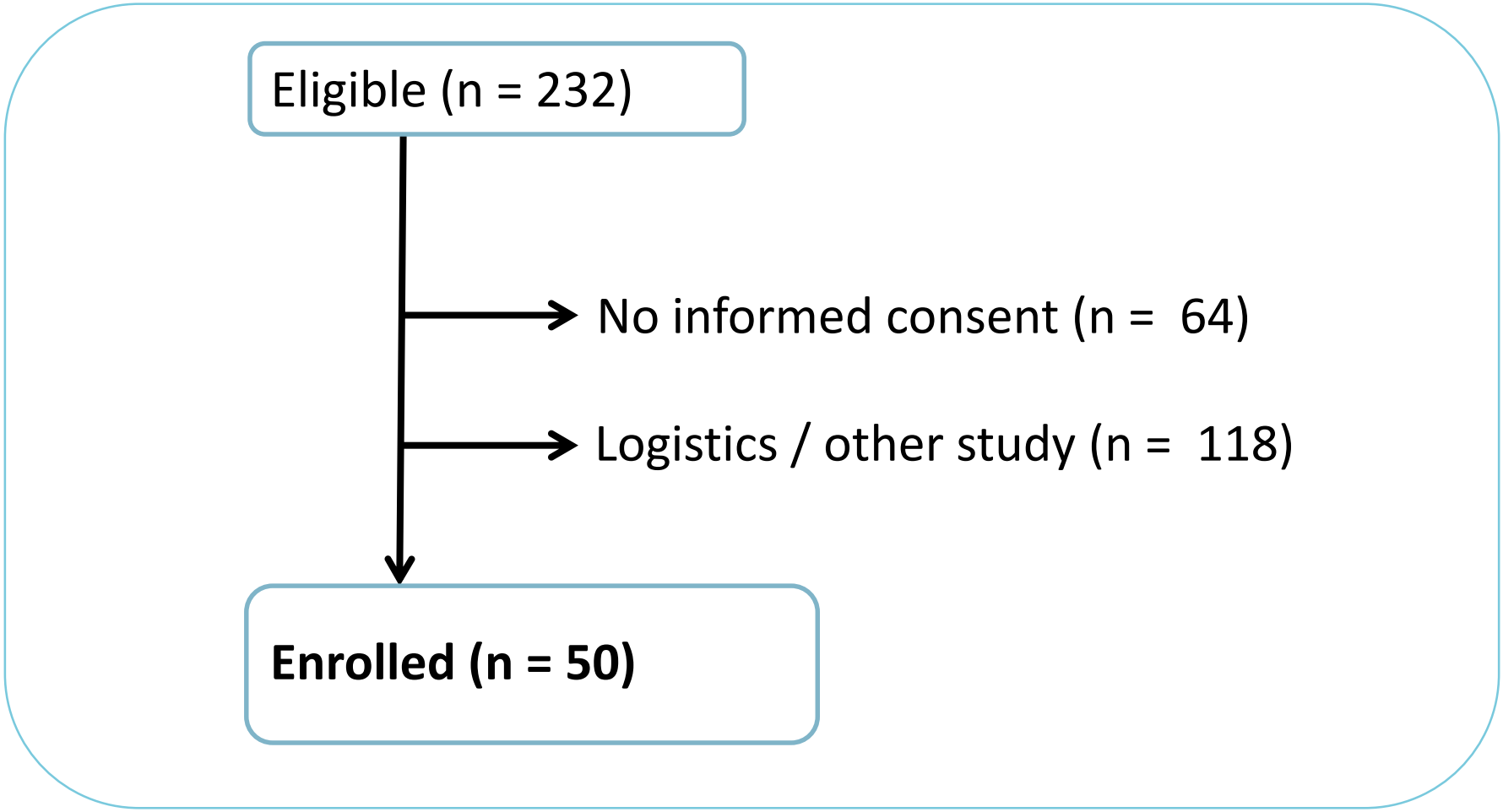
Aim: To study the **impact of age** on intestinal and hepatic **CYP3A** or **UGT** activity using the oral and IV clearance of **midazolam** or **paracetamol,** respectively

Design: PK microtracer study, 0-6 yrs of age, n=60, each drug



TNO the Netherlands - AMS facility

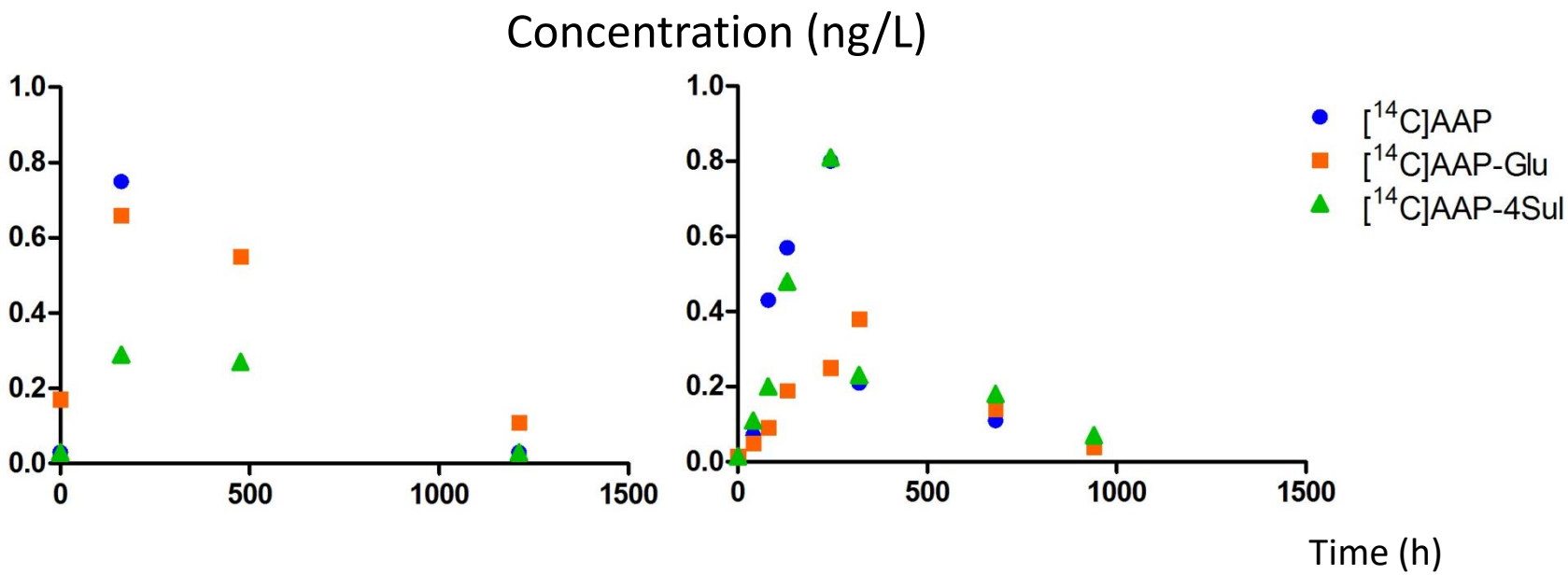
^{14}C-Paracetamol microtracer study



Detectable [^{14}C]paracetamol and metabolites

Patient 1 age 3.6 months

Patient 2 age 10.6 months



Mooij, Clin Pharmacokin, 2014

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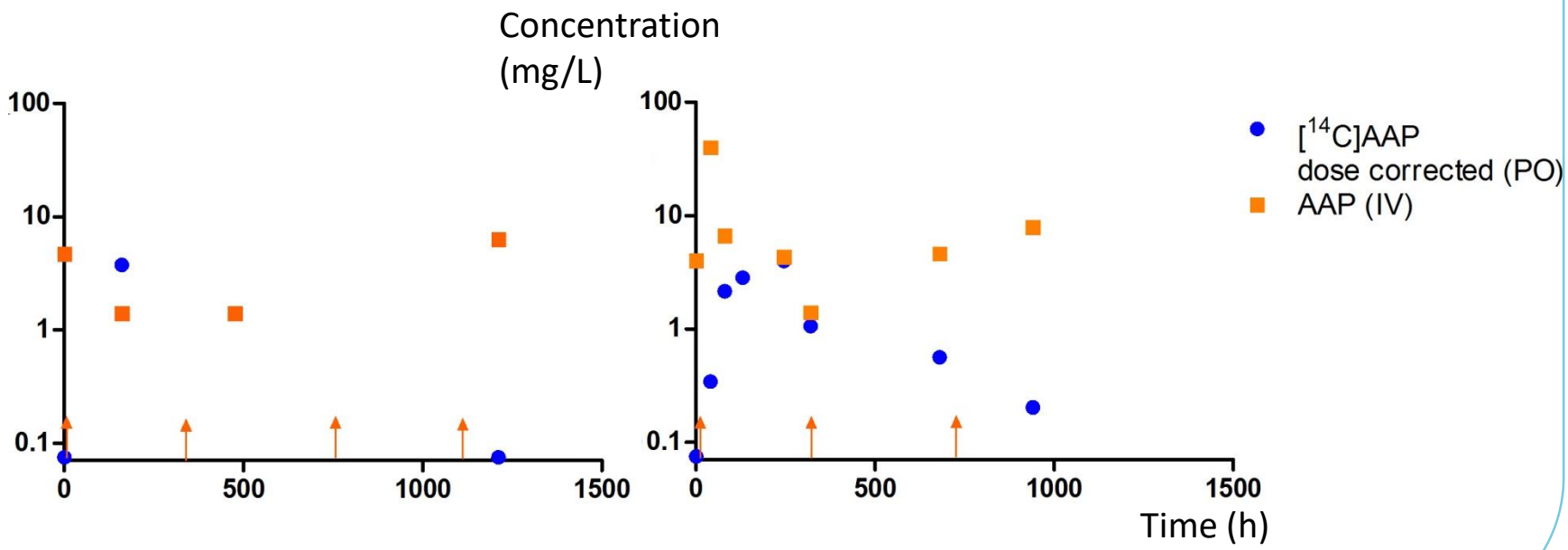
Dose linear?

Patient 1 age 3.6 months

Patient 2 age 10.6 months



Mooij et al, Clin Pharmacokin, 2014

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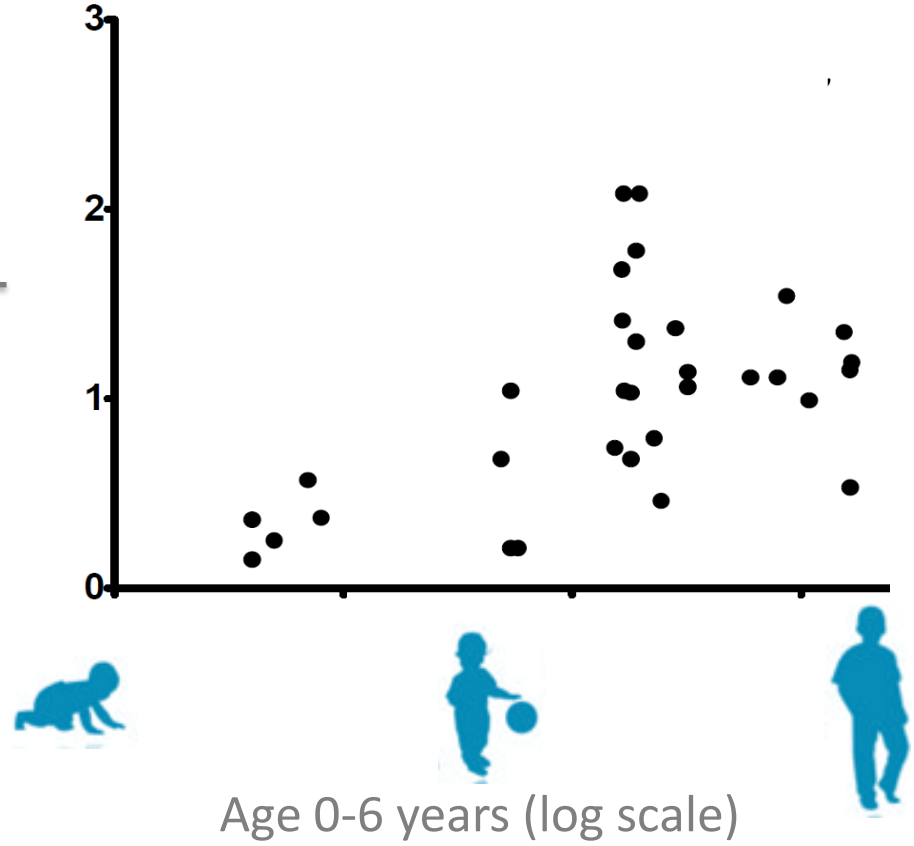
Age affects paracetamol metabolism

$AUC_{0\text{-}inf}$ $\frac{AAP\text{-}Glu}{AAP\text{-}Sul}$



Mooij et al, Clin Pharmacokinetic, 2017

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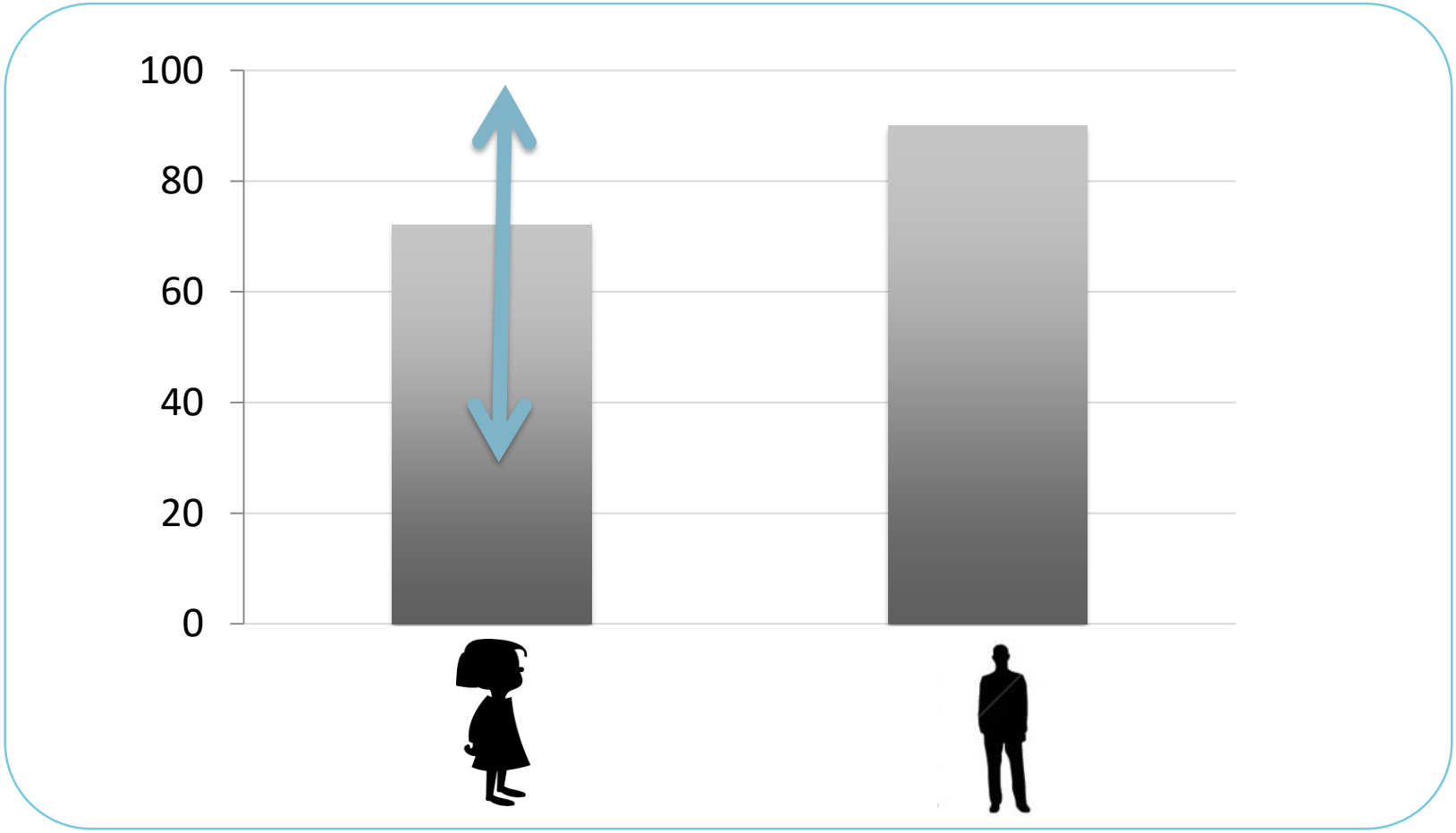
Oral bioavailability in children lower?



Kleiber et al. In preparation

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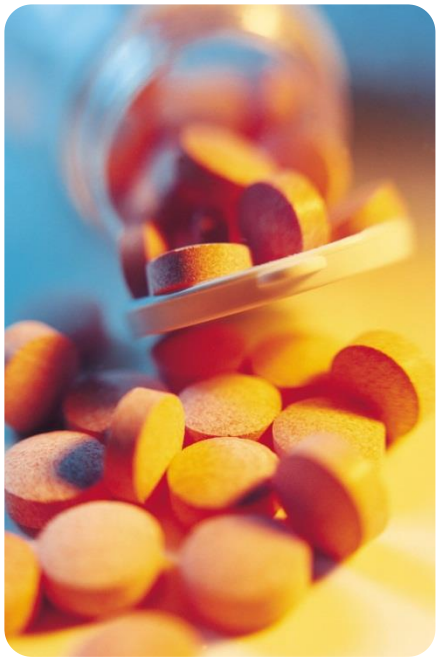
Challenges for microdosing studies

- Choice of probe drugs
  - dose linearity
  - specific for pathway
- Manufacturing
- Costs
- Perceived radiation risk
- Recruitment
- Practical issues (sampling)



Future opportunities

- Other special populations
  - Pregnancy,
  - Dementia
  - Critically ill
- Metabolites In Safety Testing (MIST)
- Industry?

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TNO innovation for life

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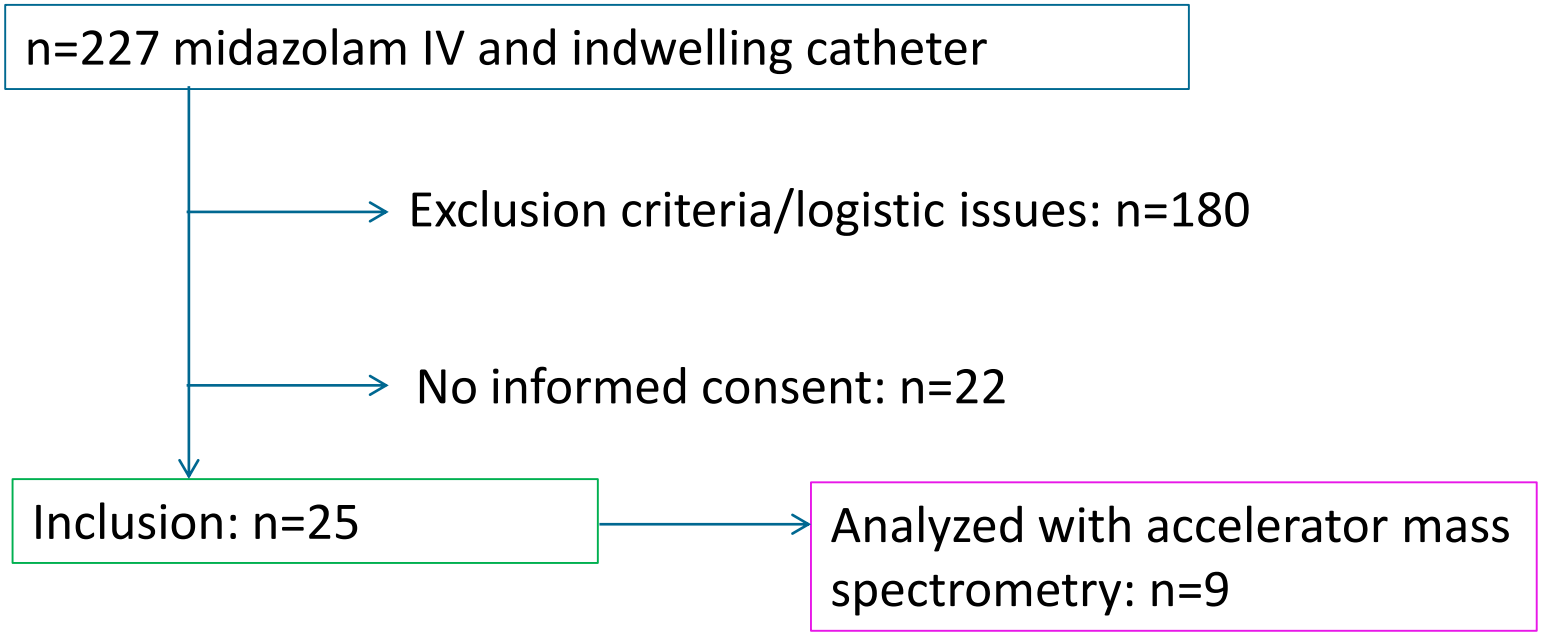
^{14}C-Midazolam: Preliminary results

October 2015 – February 2017



TNO innovation for life

Dose linearity?

	De Wildt et al	Our study	Reed et al
Age	Preterms	0 – 6 yr	6 mth – 16 yr
Cmax mida (ng/ml)	161 (38-510)	99.8 (17.6 – 287.1)	55.6 ± 30.2
Cmax OHM (ng/ml)	25.8 (<0.1-55.3)	12.5 (6.0 – 98.0)	35.6 ± 19.7
AUC Mida (ng/h/ml)	1532 (225-5715)	659 (47- 1394)	137± 86
CL Mida (L/h/kg)	0.16 (0.04–0.93)	0.4 (0.2 – 5.3)	3.0 ± 1.4

De Wildt et al. Br J Clin Pharmacol, 2002., Reed et al. J Clin Pharmacol, 2001.

Effect of age and disease?

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Midazolam preliminary results - example