

Day 2 Exercise 1a

One-compartment isolated perfused liver model

A Course on Physiologically Based Pharmacokinetic (PBPK)
Modeling in Drug Development and Evaluation

April 6-10, 2009

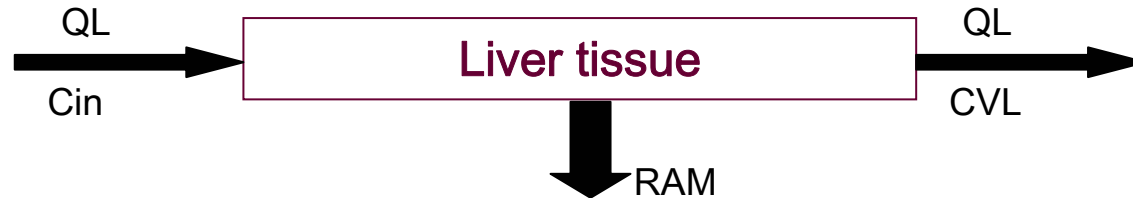
Center for Human Health Assessment
Center for Drug Safety Sciences



Limitations related to either blood flow or liver metabolism

- In this Clearance exercise, we will look at the metabolism of two different compounds in a liver compartment.
- By the end of this exercise, you will be able to distinguish “flow-limited” from “biochemical-limited” metabolism.

Flow-limited clearance



$$AL' = QL \cdot (Cin - CVL) - RAM$$

$$\text{Init } AL = 0.0$$

$$CL = AL/VL$$

$$CVL = CL/PL$$

$$RAM = AM'$$

$$AM' = (CVL \cdot V_{max}) / (CVL + K_m)$$

$$\text{Init } AM = 0.0$$

AL' = rate of change of amount in liver (mg/h)

Init AL = initial amount in liver (mg)

CL = liver concentration (mg/L)

CVL = concentration in liver venous blood (mg/L)

QL = regional blood flow to liver (L/h)

PL = liver:blood partition coefficient (unitless)

VL = liver volume (L)

V_{maxc} = maximum metabolism rate (mg/h)

K_m = Michaelis-Menten constant (mg/L)

$RAM = AM'$ = rate of change in amount metabolized (mg/h)

More on the Michaelis-Menten equation

$$AM' = (CVL * V_{max}) / (CVL + K_m)$$

AM' = rate of change in amount metabolized – mg/h

CVL = concentration in liver venous blood – mg/L

V_{max} = maximum metabolism rate – mg/h

K_m = Michaelis-Menten constant – mg/L

When a compound's concentration is much higher than K_m, the rate of metabolic clearance (AM') becomes a constant. Do you know what it is?

When a compound's concentration is much lower than K_m, the rate of metabolic clearance (AM') becomes a 1st order clearance. Can you write down that equation?

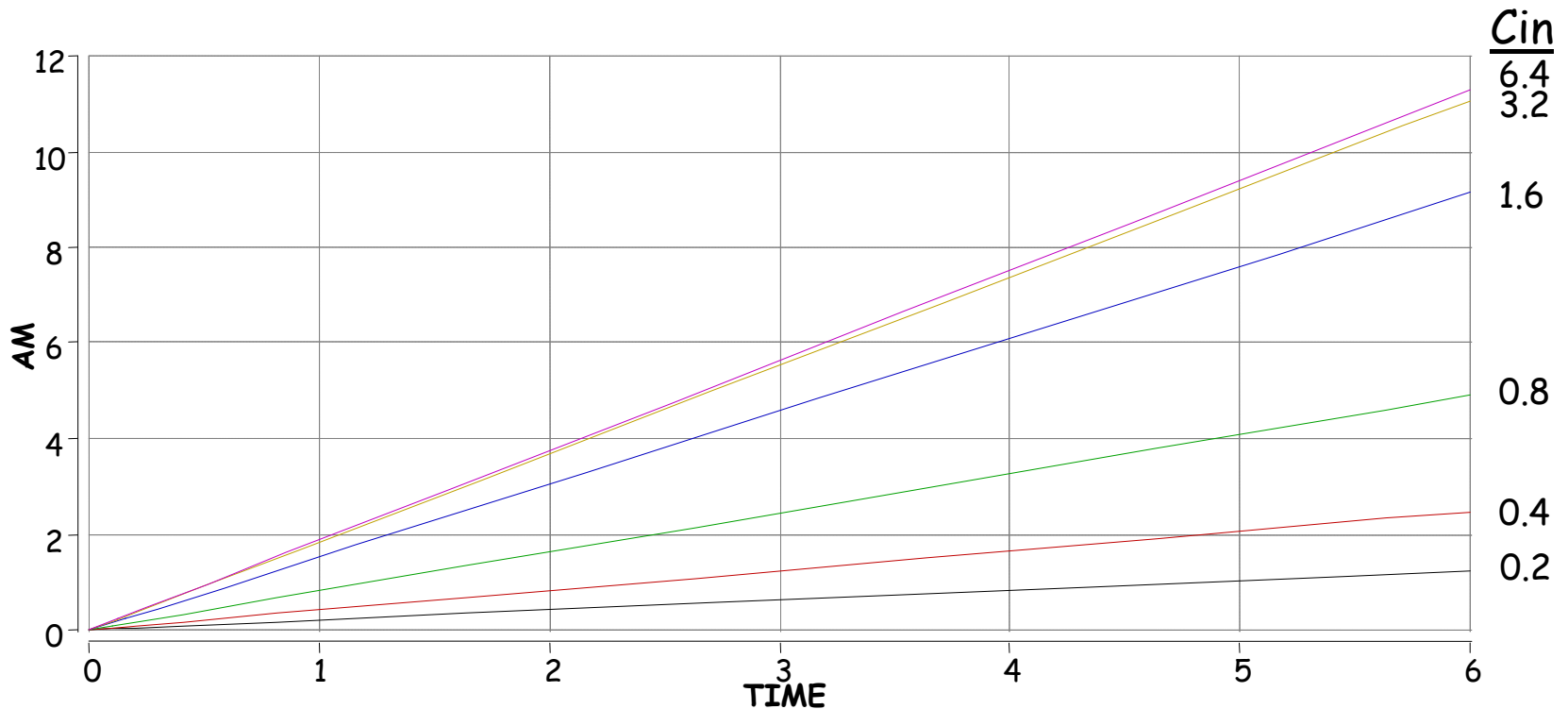
Flow-limited clearance

Compound 1

- Step 1: Open liver.mmd and examine model code
- Step 2: Add equations for metabolism
- Step 3: Run model for compound 1 (cpd1)
 - Compound 1 binds enzyme w/ high affinity
 - In Parameter window, set $V_{maxc} = 5.0$ & $K_m = 0.2$
- Step 4: Run the model at various input concentrations (C_{in}) and examine the effect on amount metabolized (AM)
 - Run at $C_{in} = 0.2, 0.4, 0.8, 1.6, 3.2, 6.4$
 - Click on Overlay in the Graph window to see the series of plots.

Flow-limited clearance

Compound 1



*Note the change in behavior between $C_{in}=3.2$ and 6.4 . At lower doses, doubling C_{in} doubles the amount metabolized, why is this not true for $C_{in}=6.4$?

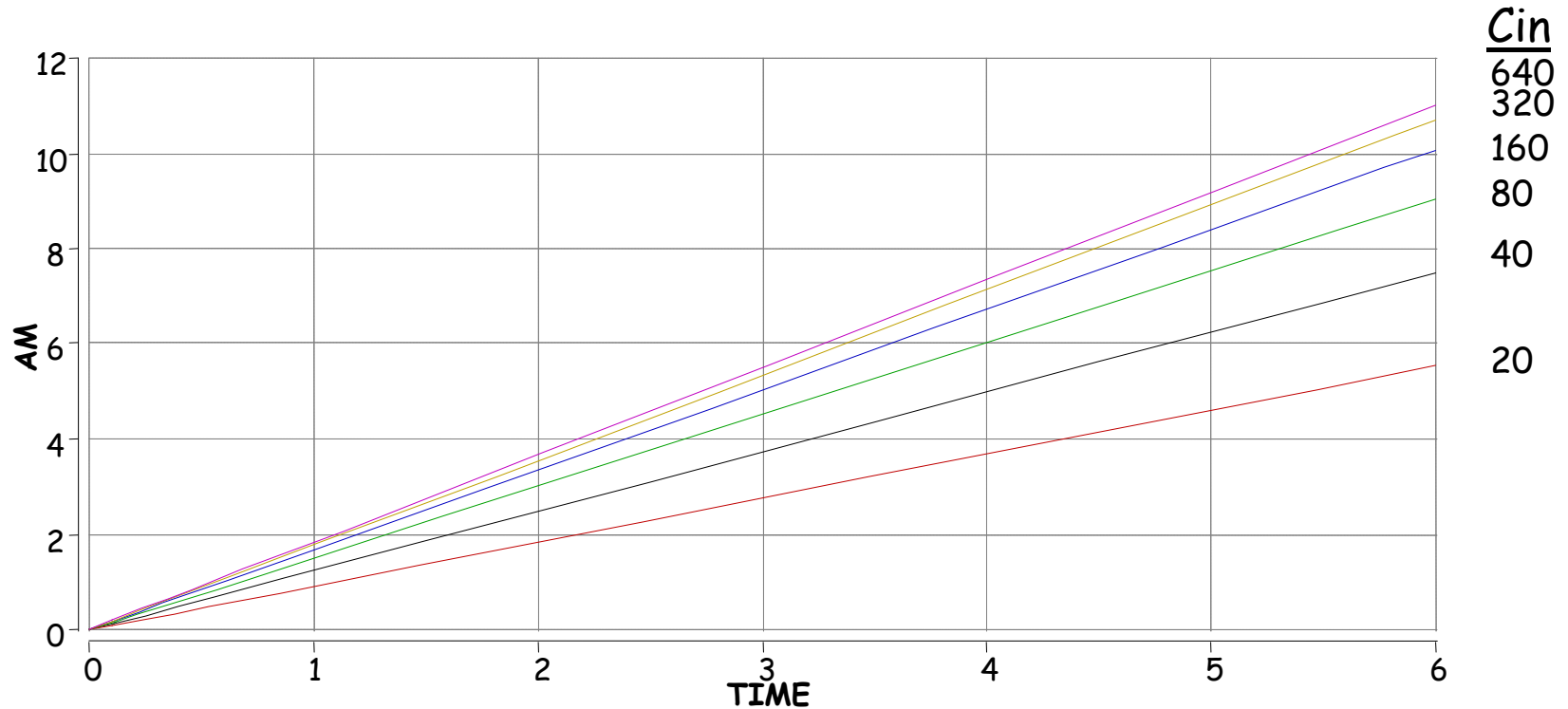
Biochemical-limited clearance

Compound 2

- Step 5: Repeat Steps 3 – 4 for compound 2 (cpd2), with the following changes
 - Compound 2 binds enzyme w/ low affinity
 - In Parameter window, set $K_m = 20$
 - Open a new Graph window
 - Go to Graph/New Window
 - Go to Graph/Choose Variable and add AM
 - Click Overlay in the Graph window
 - Run at $C_{in} = 40, 80, 160, 320, \text{ and } 640$
 - Note that K_m/C_{in} is the same for both compounds

Biochemical-limited clearance

Compound 2



For compound 1, at lower doses, doubling C_{in} doubles the amount metabolism (AM). This observation is not true for compound 2. What does the figure above tell you about the control of metabolism of compound 2?

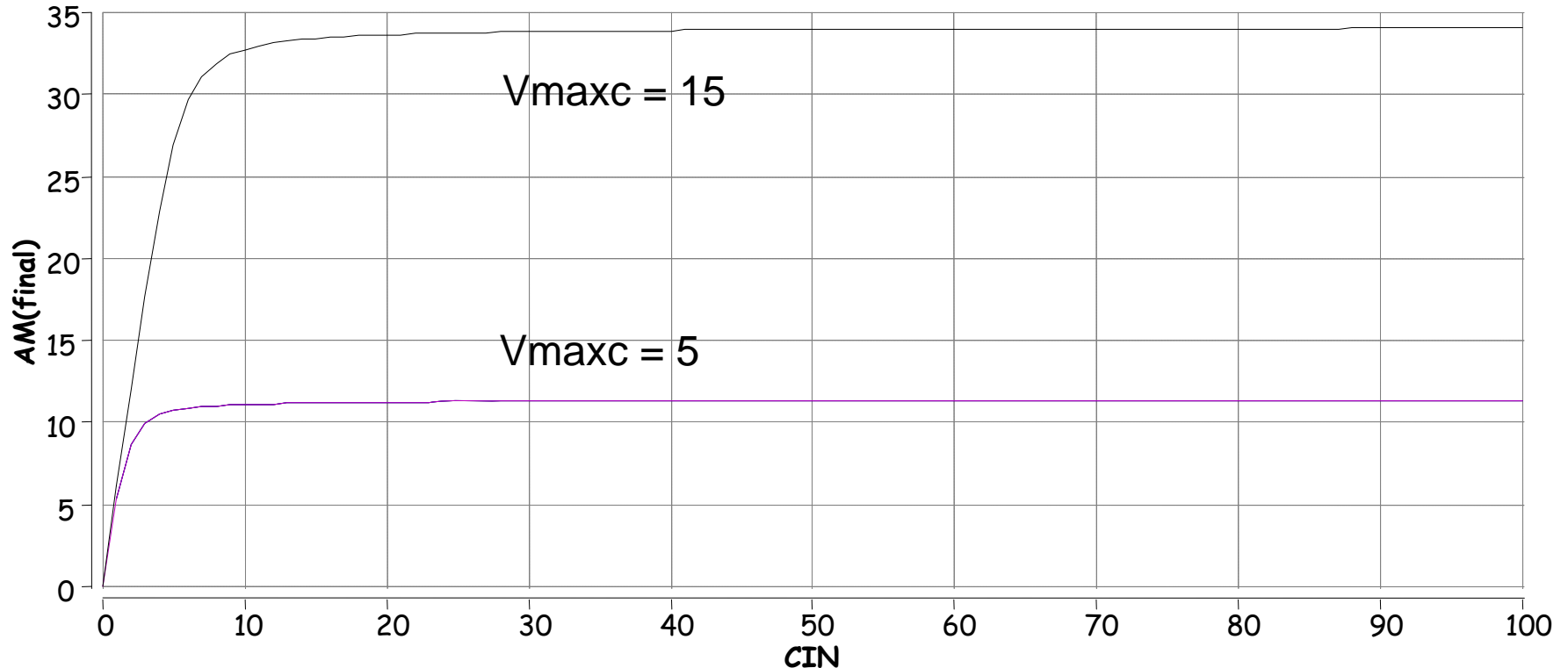
Vmax, Km and Dose-response

- Is the different dose-response behavior observed for compounds 1 and 2 due to different Km values (0.2 vs. 20)?
- How about the impact of Vmax on dose response?
- Let us examine Vmax's impact on dose response directly with parameter plots.

Parameter plots

- Step 6: Go to Parameters/Parameter Plot
 - Choose 'Parameter' = C_{in} .
 - Set initial and final C_{in} (e.g., 1 and 100) and # of runs (e.g., 100).
 - Choose 'geometric'.
 - Choose 'Variable' by adding AM.
 - Click 'final'.
 - Run parameter plot for $K_m = 0.2$, $V_{maxc} = 5$.
 - Run parameter plot for $K_m = 0.2$, $V_{maxc} = 15$.

Dose-response for compounds with the same K_m , but different V_{max}



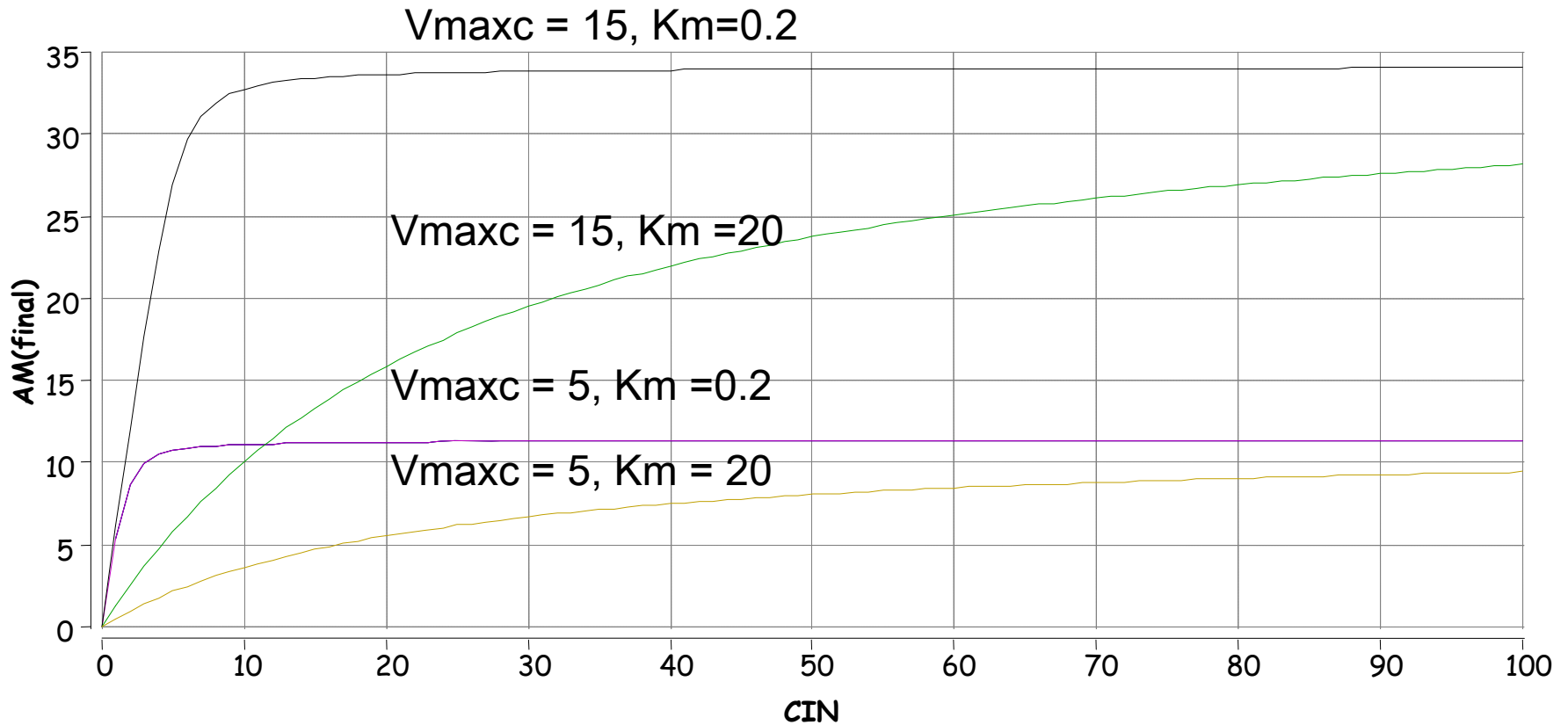
What do you say is the effect of V_{maxc} on clearance?

Vmax, Km and Dose-response

- Now that we understand how Km and Vmax each influence the relationship between dose and the amount metabolized, let us look at the influence of both parameters together.
- Step 7: Run parameter plots
 - Repeat for Km = 20, Vmaxc = 5.
 - Repeat for Km = 20, Vmaxc = 15.

Dose-response curves for four compounds

$K_m = 0.2$ and 20 , $V_{maxc} = 5$ and 15

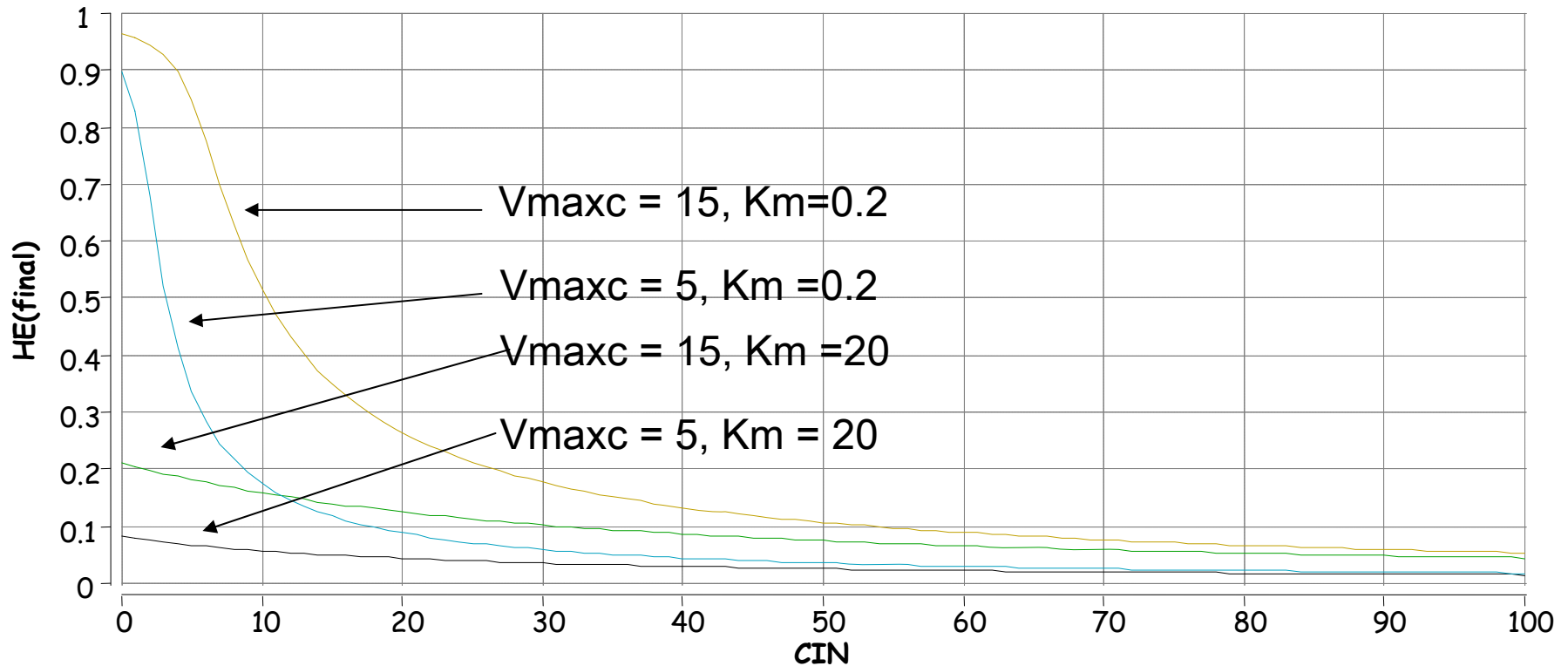


Vmax, Km and Hepatic extraction

- We can also observe the impact of Vmax and Km on the relationship between dose and hepatic extraction (HE; %dose removed by metabolism).
- Step 8: Go to Parameters/Parameter Plot.
 - Choose 'Parameter' = Cin.
 - Set initial and final Cin (e.g., 1 and 100) and # of runs (e.g., 100).
 - Choose 'geometric'.
 - Choose 'Variable' by adding HE.
 - Click 'final'.
 - Run parameter plot for Km = 0.2, Vmaxc = 5.
 - Run parameter plot for Km = 0.2, Vmaxc = 15.
 - Run parameter plot for Km = 20, Vmaxc = 5.
 - Run parameter plot for Km = 20, Vmaxc = 15.

Dose-response curves for four compounds

$K_m = 0.2$ and 20 , $V_{maxc} = 5$ and 15



Why would HE decrease with dose, as opposed to AM?