4 Toxicokinetics

Andrew Gordon Renwick

CONTENTS

Excretion via the Gut

The bile is the most important route allowing foreign compounds to move from the general circulation into the gut. The biological aspects of this mechanism have been reviewed [47], and certain pertinent points have emerged. Organic cation transporters on the sinusoidal membrane transfer large polar cations into the hepatocyte and from the hepatocyte in the bile [40,45]. The bile may be regarded as a complementary pathway to the urine, with small molecules being eliminated by the kidney and large molecules in the bile; thus, the bile becomes the principal excretory route for many xenobiotic conjugates. Species differences exist in the molecular weight requirement for significant biliary excretion, which has been estimated as 325 ± 50 Da in the rat, 440 ± 50 Da in the guinea pig, 475 ± 50 Da in the rabbit, and about 500 Da in humans. In the rat, small molecules (less than 350 Da) are not eliminated in the bile, and large molecules (more than 450 Da) are not excreted in the urine, even if the principal excretory mechanism is blocked by ligation of the renal pedicles or bile duct, respectively. Compounds of intermediate molecular weight (350 to 450 Da) are excreted by both routes, and ligation of one pathway results in increased use of the other [48].

Foreign compounds may also enter the gut by direct diffusion or secretion across the gut wall, elimination in the saliva, pH partitioning of bases into the low pH of the stomach, and elimination in the pancreatic juice. In most cases these routes are quantitatively of minor importance, although diffusion into fecal fat is the main route of elimination in humans for polyhalogenated compounds, such as TCDD, which are resistant to metabolism. Transfer from the blood into the gut lumen may play an important role in toxicity by allowing a foreign compound to undergo metabolism by the gastrointestinal flora [49]. The toxicological implications of the gut microflora have been reviewed by Scheline [19].

MATHEMATICAL PRINCIPLES

To describe adequately the changes in blood or plasma concentrations of foreign compounds, it is necessary to assign a suitable mathematical model that accurately describes the shape of the plasma concentration–time curve; however, certain aspects are model independent and are considered first, because they are usually constituent parts of the various mathematical models. In recent years, there has been a marked trend away from multicompartmental mathematical analysis, which offers little apart from mathematical predictability, toward physiologically more relevant model-independent concepts such as clearance [13,50]. Physiologically related parameters such as clearance and bioavailability represent an intermediate stage between mathematical multicompartment models and full physiologically based pharmacokinetic (PBPK) models.

Model-Independent Considerations

Biochemical and physiological processes are usually either zero-order or first-order reactions. In zero-order reactions, the rate of change in concentration with time occurs at a fixed amount per unit of time:

$$\frac{dC}{dt} = k$$

where C is concentration, t is time, and k is a constant with units of amount per time (e.g., μg/min). In first-order reactions, the rate of change in concentration is proportional to the concentration of the chemical available for the reaction:

$$\frac{dC}{dt} = kC$$

where k is a constant that represents a proportional change with time and has units of time^{-1} (e.g., min^{-1}).

Most kinetic processes (e.g., diffusion, carrier-mediated uptake, metabolism, excretion) are first-order reactions at low concentrations. *Most of the equations given below make this assumption.* Zero-order reactions are particularly important at high concentrations, when enzymes are working at maximum rate and an increase in C cannot result in an increase in rate. This situation produces nonlinear or saturation kinetics, which can assume considerable importance in toxicity studies, as is discussed below.

First-order reactions can be described by equations that include exponential functions. In many cases, the entry of a foreign compound into the body or into a tissue follows an exponential increase, which may be described mathematically by:

$$\text{Uptake} = 1 - e^{-kt} \qquad (4.1)$$

where the uptake is the concentration present at time t divided by the final concentration when all the compound has entered the body or tissue. This equation assumes that no elimination process is occurring. The elimination of a compound (by a single mechanism) once it has entered the body or tissue may be described by an exponential with a negative slope:

$$C = C_0 e^{-kt} \qquad (4.2)$$

where C is the concentration present at time t, and C_0 is the initial concentration. In Equation 4.1 and Equation 4.2, k is the rate constant for that process.

Exponential equations of the type given in Equation 4.2 may be solved as:

$$\ln C = \ln C_0 - kt$$

this can then be verified experimentally. In this case, the model serves as a tool in designing experimental studies that allow efficient resource utilization and maintaining a focus on human health risk assessment endpoints.

Unlike the mandated mathematical models used in conventional risk assessment, the biologically based dosimetry and response models are versatile and often, but not always, difficult to validate. In contrast to the mandated models, which are useful only for generating a risk number, the biologically based models allow integration of various observations, identification of critical data gaps, and estimation of risk numbers, along with attendant appreciation of areas of significant biological uncertainty [65].

QUESTIONS

1. Calculate the fat–blood partition coefficient for chemicals with $P_{o:w}$ values of 1, 100, or 1000. Interpret your results.
2. Develop a conceptual representation of a PBPK model for *n*-octane ($P_{o:w}$ = 151356, $P_{w:a}$ = 0.00762).
3. Calculate the alveolar ventilation rate (Q_p) for a human weighing 64 kg, knowing that the body-weight-normalized Q_p for mammals is 15 L/hr/kg.
4. The V_{max} and K_m of pyrene determined *in vitro* using rat liver postmitochondrial fractions were 5.935×10^{-4} μmol/min per mg protein and 27.73 μmol/L, respectively. Convert these potentially useful *in vitro* values for incorporation within a PBPK model for the rat (protein concentration = 88 mg protein per g liver; liver weight = 10g).
5. Using the rat PBPK model presented in Figure 5.25 of this chapter, determine the external exposure concentration of styrene corresponding to an area under the liver concentration vs. time curve (AUC) of 150 μg·hr/L (for the parent chemical). Set the exposure duration to 6 hr and the length of simulation to 24 hr.
6. Determine the human exposure concentration of styrene that yields the same AUC in animals (i.e., 150 μg·hr/L). Set the exposure duration and length of simulation to 24 hr.

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