Appendix E

Calculation of Blood Levels from Exposure to 5.0 mg/m^3 MEK (IRIS inhalation reference concentration)

Appendix E. Methyl Ethyl Ketone in Human Blood

Blood Concentration of MEK Relative to MEK RfC

Tissue concentrations resulting from exposure to volatile organic chemicals (VOCs) can accurately be estimated with either physiologically based toxicokinetic (PBTK) models or PBTK-based simplified algebraic equations (Pelekis et al., Toxicol. Meth. 7:207-228, 1997).

For the estimation of methyl ethyl ketone (MEK) blood concentration in humans exposed to RfC levels, the following equations were used:

CV_{SS} = CA_{SS}*(QC - QL*E) / QC
CA_{SS} = CI / {(1/PB) + (QLC*E)}
E = [(Vmax/Km)] / [QL + (Vmax/Km)]

where:

- CV_{SS} = Concentration in venous blood at steady-state (mg/L)
- CA_{SS} = Concentration in arterial blood at steady-state (mg/L)
- QC = Cardiac output (L/hr)
- QL = Blood flow to the liver (L/hr),
- E = Hepatic extraction ratio
- CI = Ambient exposure concentration (mg/L)
- PB = Blood:air partition coefficient
- QLC = Blood flow to the liver (expressed as fraction of cardiac output, L/hr/kg),
- Vmax = Maximal rate of metabolism (mg/hr)
- Km = Michaelis-Menten constant (mg/L)

The calculations of blood concentration at steady state in humans exposed to 1 mg/m^3 (=1E-03 mg/L air) of MEK are shown below. Data were obtained from Perbellini et al. 1984 and Liira et al. 1990.

QL = 81.02 L/hr
CI = 1 mg/m^3 = 1E-03 mg/L = 0.34 ppm
PB = 183
QLC = 0.23 L/hr/kg
Vmax = 30 μmol/min = 130 mg/hr
Km = 2 μmol/L = 0.144 mg/L
BW = 70 kg

Step 1: Calculation of extraction efficiency

E = [(Vmax/Km)]/[QL + (Vmax/Km)] = [(130/0.144)]/[81.02 + (130/0.144)] = 0.9176

Step 2: Calculation of CA_{SS}

$$CA_{SS} = \frac{CI\ (mg/L)}{(1/PB) + (QLC*E)} = \frac{1E\text{-}03}{(1/183) + (0.23*0.9176)} = 0.004618\ mg/L$$

Step 3: Calculation of CV_{SS}

$CV_{SS} = CA_{SS}*(1 - QLC*E) = 0.004618 *[1 - (0.23*0.9176)] = 0.003643$ mg/L = 0.003643 ppm

The venous blood concentration of MEK following continuous exposure to 1 mg/m^3 of MEK is 0.003644 mg/L or 0.003644 ppm. In converting mg/L to ppm of MEK in blood, no adjustment factor is needed.

Based on the above calculation, the inhalation RfC of 5 mg/m^3 would equate to a blood level multiple: **(5) X (0.003644 ppm) = 0.01822 ppm (18.2 ppb)** in the blood. Liira et al. (1990) used a physiologically based pharmacokinetic model to estimate that MEK metabolism would be saturated at airborne MEK concentrations of 50 ppm during exercise and 100 ppm at rest. Therefore, the inhalation RfC of 5 mg/m^3 (equivalent to 1.7 ppm) would result in blood levels of MEK well below the metabolism saturation levels.

REFERENCES

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